IN THE UNITED STATES DISTRICT COURT

IN AND FOR THE DISTRICT OF DELAWARE

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IN RE BRIMONIDINE PATENT LITIGATION) **C.A. 07-md-1866-GMS**

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Wilmington, Delaware
Monday, March 9, 2009
9:00 a.m.
Day 1 Trial

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BEFORE: HONORABLE GREGORY M. SLEET, Chief Judge

APPEARANCES:

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THE COURT: Good morning, counsel. Please be seated.

(Counsel respond "Good morning.")

THE COURT: I see we have a cast of thousands. Please, take your seats.

Mr. Marsden, would you like to do the honors?

MR. MARSDEN: Thank you, Your Honor. Good morning. William Marsden from Fish & Richardson. To my immediate left is Jon Singer, also from Fish & Richardson. To [his see left is Juanita Brooks, also from Fish & Richardson.

If I could introduce two representatives of our client in, the back, Bill Sharp, who is the chief litigation counsel at Allergan, and Martin Borit (phonetic), who is the chief intellectual property counsel.

THE COURT: Good morning.

Mr. Cottrell.

MR. COTTRELL: Good morning, Your Honor. Fred Cottrell for Exela. With me at counsel table, Jeff Boggs, and Sharon Crane, Erin Dunston in the back.

I think Mr. Boggs would like to introduce our client who is here today.

THE COURT: That is fine.

MR. BOGGS: Yes, Your Honor. With me today, I have the founder and the president and CEO of Exela

Bio-Cide, Dr. Koneru.

THE COURT: Welcome to Delaware, sir.

MR. MOORE: Good morning, Your Honor. David Moore from Potter Anderson. With me today from Katten Muchin are Robert Breisblatt, Steven Benson, and Brian Sodikoff.

THE COURT: Good morning. Welcome back, all of you.

Counsel, a few items we should discuss. We have eight days. What I am thinking is, the typical day will go roughly from 9:00 to 5:00. And this is going to be a timed proceeding. We will take probably a morning break at some point, and an afternoon break. We will take an hour for lunch, roughly around 12:30 usually.

That works out, by my estimate, to roughly six and a half hours a day. That is the multiplier, it will be six and a half times eight divided equally, unless there is some discussion we need about that.

MR. BREISBLATT: Your Honor, when you say "equally," do you mean equally among each of the three parties?

THE COURT: Mr. Marsden.

MR. MARSDEN: We have had an exchange on this. Defendants have proposed 60/40, with defendants getting 60 percent of the time. We would argue the other way around

would make more sense, because we have 11 witnesses, they have, collectively, five. We offered 50-50, 50 for Allergan, 50 for the defendants. They have raised six of the same defenses. One would hope that they are not going to repeat the evidence on those defendants, so there should be no overlap. We need to prove our invention story, prove our infringement against Exela, and respond to this kitchen sink they have collectively raised.

We think 50-50 is a fair allocation.

MR. BREISBLATT: Your Honor, the reason we said 60-40 is, frankly, we have five patents that we have the burden on. We have the higher burden. We have more patents to go on, Apotex. We are going on invalidity of, like I say, all patents at issue. We think the 60/40, with us and Exela probably splitting 30/30 makes the most sense. They still get 40. They still get more than the two of us individually.

Remember, this started off as an individual case.

THE COURT: Both positions are very reasonable, counsel. Mine is more. So it will be 50-50.

Again, multiplier is six-and-a-half times eight. You will keep time on one another, we will back you up.

Anything else?

Let's go. Ms. Brooks, are you ready?

MS. BROOKS: I am ready, Your Honor.

Good morning, Your Honor. Counsel, may it please the Court.

Your Honor, this is a case about a medication that Allergan produced called Alphagan P. As a result of the inventions that occurred during the formulation of Alphagan P, the United States Patent and Trademark Office issued four patents that covered those inventions.

In addition, there was a preservative used in Alphagan P called Purite. That preservative had already been awarded a U.S. patent several years before, before the combination of the Purite with the Alphagan.

THE COURT: You might want to use the mike so everybody can hear you, Ms. Brooks.

MS. BROOKS: Thank you, Your Honor.

What is this case about? What does Alphagan P do?

Alphagan P is used for the treatment of glaucoma.

THE COURT: Is there anything you would like me to have?

MS. BROOKS: My apologies, Your Honor. We should have had those ready to go.

What is glaucoma? Glaucoma is a disease of the eye that, if left untreated, can eventually cause blindness.

This is, as Your Honor can see, there is an arrow right here to show the very early stages of glaucoma, what happens. You begin to get blurring on the outside of your vision.

If glaucoma is left untreated in the intermediate stages, as you see here, there is substantial blurring that occurs. There is only clarity in the center. Again, if it is left untreated, it goes to the advanced stages, you end up hardly seeing anything, and, in fact, it could cause, eventually, blindness.

This I gathered from the American Health Assistance Foundation, off of the Internet. If you look up glaucoma, this is how it is described to individuals. This is the eyeball.

Right here we have, it is hard to read, zero ciliary body and muscle, iris, the lens, the cornea.

What happens in glaucoma, and they are not sure exactly why, there is a buildup of aqueous humor fluid here in the front of the eye. What that causes is the eye then to be compressed and pressure to build up inside the eye.

Your Honor is going to hear this term throughout this case, intraocular pressure, which is also known as IOP. What happens in glaucoma is that an individual suffering from glaucoma will have elevated intraocular pressure, or elevated IOP.

If it is left untreated, that pressure will damage the optic nerve that is back here. And the optic nerve is essentially the cable that runs to the brain, enabling one to be able to see and translate the sights that are coming in through the eye.

If that optic nerve is damaged to such an extent, one could actually become blind.

So it is very important, if possible, to get that intraocular pressure lowered, thereby preventing the damage to the optic nerve.

How is that done? This is a very busy chart. It is just to show Your Honor the industry that is out there for the treatment of glaucoma. There are all sorts of medications that are presently being marketed. And they have different mechanisms of action. Up here, the first ones we have are what are called beta-adrenergic receptor antagonists, also known as beta-blockers. There is a medication called Timoptic that is out there, in that category, Betimol, Betoptic-S, they are manufactured by different companies.

That is a different mechanism of action than Alphagan P. Alphagan P is located down here in the third category. It is an alpha-2-adrenergic receptor agonist and it has a different mechanism of action than, for example, the beta-blockers do or the next category, which are the

prostamides, or this category down here called the prostaglandins.

Each of these categories have their own risks and benefits. Beta-blockers can be very successful in lowering IOP in the eye. The problem is if it is absorbed systemically, a lot of the elderly glaucoma patients are already on beta-blockers for heart problems they may be having, then you have a combination of beta-blockers in your eye with beta-blockers in your body and it could turn out to have very bad side effects. Each of these have their ups and downs.

The alpha-2-adrenergic receptors in this case, the alpha-2-adrenergic agonists, with brimonidine tartrate, that is the active ingredient that is in Alphagan P ,Dr. Whitcup, who will be our first witness, will explain the mechanism of action of brimonidine tartrate and how it works to lower intraocular pressure in the eye.

Alphagan P was not the first medication to have brimonidine tartrate as the active ingredient. The first medication to have brimonidine tartrate as the active ingredient was Alphagan.

Alphagan, as disclosed in the prosecution history of the patents in suit, had two characteristics of it that turned out to make it not as beneficial a drug as it could be.

Alphagan, the original Alphagan, first of all, had .2 percent brimonidine. That was the amount of active ingredient. In addition to that, it was formulated at a pH of about 6.3 to 6.5. And that will become very important later as we get into the details of the patents.

But it was a successful drug. It lowered intraocular pressure. It had some side effects, but they weren't so substantial that it made it a completely ineffective drug or unsafe drug. But it wasn't, certainly, as effective and as safe as it could be.

Now, why was it not? This, Your Honor, this next PowerPoint is the pH scale, and the pH scale runs essentially from 0 to ten. As we go down the pH scale, a lower pH gets more acidic. As we go up the pH scale for a substance, it's more alkaline, or it's called base.

I don't know if Your Honor remembers the basic science classes where you put the litmus paper in and it turned red or it turned blue, letting you know if you had an acid or base. The pH of the eye is almost at neutral. Seven is neutral. The pH of the eye is 7.4. So in formulating an ophthalmic, it certainly would be a good idea if possible to try to keep that ophthalmic as close to the pH of the eye as possible. That certainly makes common sense. If you get too low, you are going to have an acidic, it is going to burn, sting. Even if you get too high, way

up on this scale, you are going to have an alkaline that, indeed, could also have a great deal of stinging and burning. It would be good if we could have an ophthalmic that is manufactured somewhere in the general pH of the eye itself.

Why wasn't the original Alphagan then at a pH of around 7.4? As Your Honor may recall, it was at a pH of 6.3 to 6.5. Why was that? The inventors in this case explained to the Patent Office why that was. It turns out that there was a characteristic of the brimonidine tartrate, which is the active ingredient in Alphagan. This is the problem with it. This comes from Column 4, Lines 15 through 19 of the '210 patent.

The solubility data for brimonidine tartrate in the formulation vehicles are presented in Table 2.

I will show that in a moment.

The results show that the solubility of brimonidine tartrate is highly pH-dependent and spans more than two orders of magnitude over the pH range of 5 to 8. The solubility decreases sharply as the pH increases.

There is a table in the patent, Table 2, that shows this solubility decreasing. If you see here, a pH of about 5.55, this is the solubility, and then as we go up, this is the solubility of brimonidine, the higher we go up the pH scale, the less soluble is the brimonidine.

So the formulators are facing that problem. What the formulators of Alphagan did is gave up on the problem, sort of, and said, All right, we won't then formulate at a pH that is higher than 7.0, that is closer to the pH of the eye. We will go down the pH scale more toward the acidic, and that way we will be assured that the brimonidine tartrate will stay in solution. And that was what the formulators of the original Alphagan did.

But the formulators for Alphagan P, Drs. Olejnik and Kerslake, who will be testifying later in this case, were given a task. They were given a task by Allergan: We want you to make a better drug. The problem with Alphagan is that the brimonidine, while successfully lowering intraocular pressure, has its own side effects. One of them is allergic conjunctivitis. That is a localized side effect, they call it.

It deals specifically with the eye and it causes the eye to become very red, very inflamed. And, essentially, once an individual develops an allergic reaction to the brimonidine, they can't take it anymore.

So it is not as if they go off the drug, the allergic reaction corrects itself, they can go back on the brimonidine. Once they develop that allergic reaction, then brimonidine is no longer a treatment option for that individual.

Now, why is that important? Because in fighting glaucoma, physicians need all the treatment options they can get. There are some individuals for various reasons that can't take beta-blockers. There are other individuals that are on the prostaglandins and they stop working.

There are other individuals on which the prostamides work to a certain extent, but they need a boost. And that's why the brimonidine is an important tool in the physician's war chest of fighting glaucoma, and to prevent the physician from being able to use that because there has been an allergic reaction of the brimonidine takes away one of their important tools.

So the formulators of Alphagan P were tasked with trying to figure out a way to increase either the efficacy and/or the safety profile from the original Alphagan. And that's what eventually led to the inventions in question.

So how did they go about it?

They went about it over the course of almost two years of research and development at Allergan. This, Your Honor, which will be introduced as PTX-289, is a document dated December of 1996. This shows some of the early formulations that the inventors tried in order to see if they could improve upon Alphagan, make it more effective and/or make it safer.

They went through -- this particular chart shows 11 different inventions -- excuse me, formulations. They tried carbopol, they tried it in a norm ophth bottle, a bottle in bottle, an ointment tube. They tried an emulsion. They tried a standard gel/carbopol combination, an Alginate gel, a certain gel, a SynerGel suspension, NanoSystems Gel, GelMed, et cetera. Why were they trying all these gels?

The defendants will argue to Your Honor that there is no invention here, that all Allergan did was take their brimonidine that they were already using in Alphagan and stick it in an artificial tear called Refresh Tears, and, boo, they called it an invention.

As you can see, they didn't do that at all. These first 11 formulations have nothing to do with Refresh Tears. And, in fact, they are all gels. Why were they working with gels?

They had a hypothesis. If you had the substance, the brimonidine, in a substance that was more viscous, it might stick to the eye longer. And if it stuck to the eye longer, then less of it would drain into what they call the nasal lacrimal duct, thereby, less of it getting into your circulatory system and systemically having systemic side effects and hopefully more of it would end up getting absorbed by the eye and getting absorbed into the cornea, which is really where you need the active ingredient

to go to lower the IOP in the eye.

They tried the gels. They tried 11 of them, back in December of '96. This one, JTX-094, is yet another iteration. We are now dealing with, the date on this is mid-'97 but the testing was actually done in early '97. We have 11 formulations they tried in late 1996. We now move on to yet an additional five more formulations that the formulators are trying.

They are testing them all against the original Alphagan. Remember, their task is, their project is, try to make it safer, try to make it more effective. What did they do?

They tried brimonidine tartrate in a different Carbopol combination with HPMC. And for the purpose of the story, we won't do all the acronyms, unless they have some importance.

They tried it with two different, Carbopol HPMC combinations, they tried it with an Aquasite gel. They tried it in suspension.

So they said to themselves, All right. We know brimonidine at higher pH's has trouble staying in solution. So maybe we will give up on a solution and maybe we will try a suspension where the brimonidine is actually just suspended in the vehicle.

Let's try that. They did it with something

called perfluorodecalin.

If you notice, at least in the gels, the pH's are all at 6.4. They have already accepted and understand that if they try to go higher, they are not going to get a solution. So they stick with -- I mean a solution, not a solution to the problem, but a solution, as in the brimonidine is going to fall out of solution.

If it falls out when it is supposed to be in a solution, you are going to end up with the equivalent of shards of glass in that medication, which we all know would not be a good thing for the eye.

Their way of dealing with the solubility problem in these early formulations -- we are now moving on -- these are five more formulations on top of the original 11. 16 formulations they have gone through. They have yet to try Fresh Tears.

They try all of these, and what happens?

What happens is this: This is the pharmacokinetics data report. What the pharmacokinetics report says is this: While the reformulations that offered an ocular pharmacokinetic advantage, however, they were cursed with a significant systemic disadvantage. Plasma concentrations were consistently higher after Aquasite and both carbopol formulations than after Alphagan.

What does that mean?

Plasma concentrations are how much brimonidine has been measured in the body where it is not supposed to be. It is supposed to be in the eye.

So something is going on. This whole theory about, wow, if we use gels, it will stay on the eye longer and it won't end up getting passed through the nasal lacrimal duct into the body, it turns out that didn't work. And, in fact, this observation, that this gel idea didn't work, and, in fact, caused even more of the active ingredient to end up in the body rather than less, was, according to David Small, both unexpected and unwanted.

And why was it unexpected and unwanted? First of all, it was unexpected because it went contrary to the idea that if you keep the gel on the eye longer, then it is going to give the eye more chance to absorb the brimonidine and it won't get into the body. So it was completely unexpected that the exact opposite happened. Why was it unwanted? Because such a phenomenon of the increase of the brimonidine in the blood, such a phenomenon in humans is going to lower the systemic safety margin. In other words, you are going to have more systemic side effects because of this phenomenon.

Now, what is a systemic side effect? I described to Your Honor what a localized side effect was, which was this allergic conjunctivitis, this red irritated

eye. A systemic side effect would be sleepiness, for example, that the brimonidine gets into the system, and while your glaucoma is treated, you turn out to be incredibly sleepy, tired, and, in fact, end up, how some of the pills say don't operate machinery, well, you are supposed to be able to operate machinery with your glaucoma medication, you are supposed to be able to drive a car, you would end up not being able to do so. So it is pretty counterproductive.

So all 16 of those formulations have to get jettisoned, it's back to the drawing board. There was nothing, unlike what the defendants say, that this was a, I believe their description is expected, easy, obvious formulation, it was just the opposite.

We now move to four more formulations.

The date on this report is March of 1998. But the actual tests on these four additional formulations, so that is four in addition to the 16 already tried, is actually done in about mid-'97. So we have worked all the way through '96, half the year through '97, trying all of these different formulations. They are not working.

Now we come to some new formulations. This is where we see the Fresh Tears. This is Alphagan, which everything is going to be tested against. Here is brimonidine tartrate in Refresh Purite.

Now we have the higher pH of 7.4. Why? Well, Refresh Purite has a pH of 7.7.

Let me stop and explain what Refresh Purite is. Refresh Purite is an artificial tear. It is manufactured by Alphagan and used in the treatment of dry eye. A lot of individuals suffer from dry eye. There is no active ingredient in it. It is essentially just a substitute for your own tears. That's why it's called an artificial tear. It has to have a preservative in it. The reason being you would use it over time, and if there is no preservative, once you use it once, once you open up the bottle of your dry eye medication, if there is no preservative, then, obviously, all kinds of bugs are going to grow in there and it's not a good thing.

So there was a preservative in Fresh Tears called Purite. And I will tell Your Honor a little more about the Purite story later when we get to that patent.

But Fresh Tears itself is this product. It is a dry eye medication. It is manufactured at about a pH of 7.7. So they took the brimonidine tartrate. They put it into the Fresh Tears product, and it ended up with a pH of about 7.4.

The formulators at this point were so convinced, there was no way that formulation was going to work because of the brimonidine tartrate solubility problems. They are

up at 7.4. It's not going to be soluble. All the tests show that. What did they do?

They add something called cyclodextrin in this formulation. Cyclodextrin is known to have solubility enhancing properties. Dr. Olejnik, one of the inventors, will explain to Your Honor why. It essentially is somewhat of a tubular structure that is hydrophobic on the inside and hydrophilic on the outside, or vice versa. I always get them backwards. And it will take the active ingredient sort of inside the tube, thereby aiding the solubility of the active.

The problem, of course, with that is that it would then possibly hang on to the active ingredient, preventing it from being absorbed into the eye, and then, once again, we have got the problem of instead of getting absorbed in the eye, it is going to go into the body and you are going to have these systemic side effects. But they put the cyclodextrin in this formulation to see if they could at least compensate for the solubility problem of brimonidine. But they were so sure that this formulation would not work, this Refresh Purite at 7.4, that they still stuck with a gel formulation, only now they were going to try it at a higher pH of 7.3, and even a castor oil emulsion. They were determined that somehow, some way, they were going to improve the safety profile of Alphagan. But it was by no

means an easy and an expected and an obvious way to go.

So now we are up to 20 different formulations that the formulators have tried in their attempts to improve the safety and efficacy profile of Alphagan.

There was another problem, why they were so kind of adverse to and thinking that using Fresh Tears in combination with the brimonidine would actually work. In addition to the pH solubility issue, there was another problem, which is the Purite. The Purite, which is the preservative that is in Refresh Tears, was known, or at least they believed, to have the potential to oxidize the brimonidine. What does that mean?

That means you take the brimonidine. You put it in the Fresh Tears, you have got your preservative called Purite. And the Purite ends up oxidizing the brimonidine, so that by the time the patient gets around to using the drug, the brimonidine has been essentially chewed up by the Purite. It doesn't work anymore. Therefore, you are not going to have an effective composition.

So they had all these problems that they were dealing with. Were they going to be able to keep the brimonidine in solution at the higher pH? Was the Purite, or was it, in fact, going to fall out as they expected it to? Was the Purite going to chew up the brimonidine, oxidize the brimonidine, thereby making it no longer an

active ingredient?

These are all documents made contemporaneously with the formulation. These aren't after-the-fact things we came up with to cover our invention story. These are what the inventors are saying to themselves back in 1998.

So now, it's, oh, mid-'98. They have been working on this for about a year. Here are our two lead inventors, Dr. Kerslake and Dr. Olejnik. And in June 1998, they write a memo to Hans Peter-Pfleger, who is in marketing, and they say to him, here is what we have done so far. More than a dozen formulations have been developed by Product Development and they have been tested both by pharmokinetic evaluation in rabbits and ultimately in humans.

And here is where we are now, mid-'98. "Based on all this different data, alternative formulations are unlikely to offer any appreciable benefits to the efficacy and safety profile of Alphagan."

In other words, our own inventors at that point are expressing skepticism that this can ever be done.

They say, you know what? This opinion is consistent with the assessment and prediction submitted by an external advisory panel of experts. So not only are inventors expressing skepticism, but Allergan had brought in an advisory panel of outside experts to say, look at what we

are trying to do here. What do you guys think?

They said, you aren't going to be able to do it. They decided that the only avenue for actually improving the brimonidine tartrate efficacy over Alphagan would be the development of a controlled ocular delivery insert, meaning to take the brimonidine and actually insert it in an insert fashion into the eye.

This is where they are in mid-'98.

But our inventors weren't willing to give up. Over all these obstacles, unwanted results, unexpected results, skepticism internally and externally, they were determined that they were going to find a way to improve the efficacy and/or safety of Alphagan.

And so they did, and that is what resulted in the patents at issue in this case, Your Honor.

This is out of the prosecution history. During the course of the formulation efforts in this case, here is what they found:

That it was particularly surprising that such a therapeutically effective dosage of brimonidine could be formulated in an aqueous solution at a pH greater than about 7.0. Figure 1 of the present specification -- and I will show that to you in a moment, Your Honor, it is in the patent -- shows the brimonidine solubility decreases precipitously at pH values above 7.0.

Actually, that is the table I already showed Your Honor, it is Table 2. The fact that a therapeutically effective dosage could be provided by a composition containing about .15 percent or less of brimonidine at such pH values is truly unexpected.

What does it say? Alphagan P ended up being brimonidine at .15 percent. Remember, Alphagan was at 2 percent. Alphagan P was at .15 percent. And it ended up being at a pH of approximately 7.2. Alphagan was at a pH of 6.3 to 6.4.

How could they have done this? How could you, first of all, get the same therapeutic effect with 25 percent less of the brimonidine? And the answer is something called the pH partition theory, that if you make a drug closer to the pH of the membrane that you are dealing with, you are going to get more of what they call the unionized version of it.

The bottom line is, it is going to allow more of the active ingredient to penetrate the membrane, thereby getting more of the active ingredient into the eye and less of it into the circulatory system.

Dr. Olejnik, who is certainly much more qualified than I to speak to this, will explain to Your Honor exactly how this unionized versed ionized works and how it fits in with pH and the level of pH.

But the second completely unexpected result was that it was staying in solution. Not only were they able to lower the brimonidine by 25 percent, they were able to keep it in solution at this higher pH. And as Your Honor saw, nobody believed that could be done.

This is the chart showing how they were able to keep it in solution. This is Figure 1 of the patent. It turns out that by combining it with Refresh Tears, what the inventors had also done was introduce a drug called carboxy -- not a drug -- a compound called carboxymethylcellulose. That is another one Your Honor is going to hear over and over again, CMC, carboxymethylcellulose. Unlike cyclodextrin, which was known to enhance solubility, carboxymethylcellulose, certainly in conjunction with something like brimonidine, which is an alpha-2-adrenergic agonist, had not been demonstrated to enhance the solubility of an alpha-2 agonist. It didn't have that tubular shape like cyclodextrin did. There was nothing about it that led the inventors to believe that it would enhance the solubility of brimonidine. In fact, it was only in there as a viscosity agent in the Refresh Tears. It wasn't in there as a solubility enhancer. But they tested. And Dr. Kerslake will talk about this testing. They tested over weeks, in fact, months, to figure out the phenomena that was going on

that enabled the brimonidine to stay in solution at these higher pH's. And they discovered this, that the CMC was enhancing the solubility of brimonidine. And that was part of the inventive features that the Patent Office granted a patent for.

And that, Your Honor, resulted in Alphagan P. Alphagan P, as Your Honor can see, is at .15 percent brimonidine. It is at a pH of approximately 7.2. And it only got there after years of work by the inventors in this case at Allergan, and overcoming hurdle after hurdle, obstacles after obstacles, skepticism upon skepticism.

This is the bottle that it comes in.

This, Your Honor, is allergic conjunctivitis that I told you about. The clinical trials of Alphagan P showed that there was a 40-percent reduction in this as a result of reducing the amount of brimonidine from .2 percent to .15, a 40-percent reduction in allergic conjunctivitis, resulting in all of these people getting to continue to use brimonidine as a treatment rather than having it taken away as a treatment option for the physicians.

This is only one of the increased safety profiles of Alphagan P over Alphagan.

Now, as a result of this increased safety profile, Allergan decided to withdraw Alphagan from the market. They now had Alphagan P. It was shown to be safer,

significantly safer than Alphagan. There was no need to have Alphagan on the market anymore.

And just to show you the continued skepticism in the industry, Allergan wants to withdraw Alphagan, which they have an absolute right to do. It is their drug. They can take it off the market. But they petitioned the FDA, in addition to that, they petitioned the FDA in a citizens' petition. And they say, FDA, we are pulling Alphagan and we are pulling it for safety and efficacy reasons because Alphagan P is so much safer than Alphagan. So we would like you to agree with us that we are pulling Alphagan for safety and efficacy reasons.

The FDA -- now, this is in May of 2003, so this is important, because this is when Alphagan P is just first out there -- the FDA is skeptical still that it could be done. The FDA says, well, you know, we have looked at the data, and we disagree with your assertion that Alphagan .15 percent is safer and/or more effective than Alphagan .2 percent and we reject your contention that Alphagan .2 percent was withdrawn for safety or effectiveness reasons.

They go on in that citizens' petition in May of 2003 to say this. Allergan had argued to them, well, wait a minute. If we weren't withdrawing it for safety and efficacy reasons, why would we withdraw it and thereby deprive ourselves of an additional income stream? And if

Alphagan P isn't significantly safer and effective than Alphagan, why are physicians choosing it over Alphagan? Why aren't they just sticking with the drug that is already out there?

The FDA answered Allergan this way, in 2003. "We find this reasoning unpersuasive. The fact that physicians have begun prescribing Alphagan P .15 now that Alphagan .2 percent has been withdrawn from the market does not support a conclusion that Alphagan P.15 percent is more effective than its predecessor. It probably reflects only the lack of available alternatives."

It makes sense. Right? It makes perfect sense. They are saying, come on, Allergan, you pulled Alphagan off the market and now you are saying, they are all prescribing Alphagan P. Of course, they are. There is no alternative. And that made sense in May of 2003.

However, in June of 2003, the generics came on the market, the generics of Alphagan, the original Alphagan. So now they are generic versions in June of 2003. So when the FDA is saying this in May of 2003, it makes sense. But in June of 2003, on come the generics. And there is the generic version of Alphagan .2 percent at a pH of 6.3 to 6.4. And now the physicians have a choice. If they don't believe that Alphagan P is significantly safer or more effective, then go and prescribe generic Alphagan.

And in June of 2003, when it hits the market, obviously, there is no prescriptions yet, so let's wait and see what happens. One of the companies that came on with the generic was Bausch & Lomb, one of the world's largest ophthalmology companies. They did a huge ad campaign, telling the physicians, we have got generic Alphagan. Alphagan P is just marketing hype by Allergan. Buy our generic. Get it cheaper for your patients. You will get the same benefit.

Here is what we saw. This is June of 2003. The data we have goes all the way out to April of 2006. This has the physicians, three years with an opportunity to start prescribing Alphagan, generic Alphagan, instead of Alphagan P. They never did it. It flattened out at ten percent, and it never changed.

The physicians have spoken. The physicians have said, oh, no, FDA, there is a significant safety advantage to Alphagan P. There is something here that is new. There is something here that is novel. There is something here that brings a benefit to our patients. And we are going to use it.

Managed care has spoken, because they could easily just take Alphagan P off the formulary and require only the prescription -- that they will pay only for generic brimonidine.

But they haven't done it, either.

And what's interesting is that is not normally what happens. If, truly, there is no difference between a drug that is out there, like Alphagan P, and a generic brimonidine, then what normally happens after the generic comes on the market is you see this (indicating), only it's literally the opposite. Recently, a glaucoma medication called Cosopt went generic, and you will hear the testimony of Joseph Schultz from Allergan, in three weeks time 90 percent of the market was prescribing generic Cosopt, three weeks they converted back.

Here we have three years and nobody is doing it.

The United States Patent and Trademark Office recognized how Alphagan P was new and novel and inventive. They were told all about Alphagan. It was right there. I showed it to Your Honor at the beginning of my opening. They were told all about Alphagan, and yet they issued four United States patents based on the various inventions that took place during the formulation of Alphagan P.

The first one was the '210 patent. This deals with compositions containing alpha-2-adrenergic agonist components. And I have put up just a representative claim. Our expert, of course, will walk Your Honor through these claims. Essentially, what the '210 patent talks about is not just alpha-2-adrenergics, but specifically brimonidine,

and the use of a polyanionic solubility enhancing component with that brimonidine, something that had not been done before.

And this is the '210 patent, Your Honor.

They also issued the '873 patent. The '873 patent deals with the broader category of alpha-2-adrenergic agonists, rather than being limited just to brimonidine, it is the broader category of the alpha-2-adrenergic agonists, in addition to a solubility enhancing component, and note, excluded is other than cyclodextrin, because cyclodextrin was known to have the solubility enhancing, so it is specifically excluded in this claim, and, an oxychloro component in an effective amount to at least aid in preserving the composition. So this is the Purite is an oxychloro component. And, of course, up until the formulation efforts of the inventors here, it was believed that you couldn't combine Purite with brimonidine. It would chew it up.

So, indeed, once again, there was an additional discovery that is covered by the '873 patent. And we are asserting, Your Honor, Claim 12, the dependent claim, to limit it even further. So it's not just an alpha-2 with an SEC with an oxychloro component, but the solubility enhancing component has to be carboxymethylcellulose.

So that is the '873 patent, Your Honor.

They also issued the '834 patent. The '834 patent is the Alphagan P formulation. It is very specific, very narrow. And it is the only patent that we are asserting, Your Honor, against Exela.

Now, Apotex will argue that all four patents are exactly the same. If that were the case, we would be asserting all four patents against Exela. But we are not. We are only asserting the '834 patent against Exela, because Exela has a different formulation than Apotex, and Exela's formulation, we are asserting, does, indeed, infringe the '834 patent. But we are not asserting that it infringes the other three patents.

So what is the '834 patent?

The '834 patent is specifically a therapeutically effective aqueous ophthalmic composition comprising up to about .15 percent of brimonidine, having a pH of about 7.0 or greater, and the brimonidine being soluble in the composition at room temperature.

So that is the formulation. That is the formulation that Exela, indeed, is going to be using, if ever allowed to by the FDA. And that is what Exela is, in fact, infringing.

We have one more patent, Your Honor, that was issued as part of the overall inventive process that went on here, the '337 patent.

The '337 patent is essentially like the '210 patent but it's broader, it is the genus versus the species. The '210 patent is limited to brimonidine. The '337 patent is limited to alpha-2 adrenergic agonists, not limited just to brimonidine, which is a subpart, a species of the overall genius of alpha-2-adrenergic agonists. It is in addition a solubility enhancing component, again, other than cyclodextrin, and we are asserting, along with Claim 1, dependent Claim 5, which limits the polymer to being an anionic polymer.

The '210 patent was limited to polyanionic polymers. Again, we are talking about the '337 is the genius. The '210 is the species. It is even more narrow. But we are asserting it in this case.

So the U.S. Patent and Trademark Office found four different inventive aspects of the formulation work that went on at Allergan. And in addition to that, there is someone else that thinks that what we did is new and novel, even though in this courtroom they will argue otherwise. That's Apotex.

Apotex has stipulated that they infringe all the asserted claims in this case. And this is their stipulation, and it's in the pretrial order, Your Honor, I won't read it. But they have stipulated that all of the claims that are being asserted against Apotex, indeed, they

infringe with their formulation.

Now, they tried not to. I will give them credit for this. They tried not to. They looked at our patents. They looked at our formulation. They said, how can we make a generic Alphagan P without using all the inventions that are in the patents?

So the first thing they did was say, how about this: Let's now use carboxymethylcellulose. Let's use PVA, polyvinyl alcohol. See if we can do that.

They couldn't. It says formulation is not possible with polyvinyl alcohol. As noted salting out occurred. The very thing I mentioned to Your Honor, the falling out of solution.

They tried to get rid of one of our inventions, they tried to not use carboxymethylcellulose, tried to substitute it with PVA, didn't work.

They tried something else. They tried something called HEC. And the problem was they had to use so much HEC to get anything going here that it took them over the FDA limits. They had to get rid of that one. There was another problem they had. It says, Please see the attachment, the pH has changed significantly. So this is another problem I have not explained to Your Honor yet. It is not just you have to get the brimonidine into the solution and keep it in the solution, but you have got to do it in all kinds of

varying conditions, because this is an eye medication. It's not going to be under controlled settings at Allergan all of the time. It is going to be used by somebody in Alaska. It is going to be flown to somebody in Europe. It is going to be used by somebody in Southern California. There are going to be temperature variations. And as a result of that, you may have shifts in pH.

Now, if you don't have a way to make sure that that brimonidine stays soluble within the solution at various temperatures and under various conditions, you are going to get that salting out. You are going to get the brimonidine bombing out, and therefore, it will no longer be effective and it will no longer be safe.

And Apotex saw in their attempts to design around patents that they were getting shifts in pH. They did a pH, an assay monitoring for the above product in the past three weeks, and the study shows pH 6.3 -- they tried to formulate at a lower pH. Okay. Let's get around one of their inventions, the 7.0 pH or higher. Let's try to formulate at a lower pH. Guess what happened? They weren't stable. The pH and preservative assay have dropped significantly after three weeks. They had to get rid of it.

So this is what they did. They simply copied, which a generic has a right to do, they just don't have a right to infringe a patent. So they copied our formulation

to a T, because it was tried and true and they knew it would work.

And so, this is where they say, right here, RLD stands for reference listed drug, that's us, Alphagan P. Formulation completed based on patent, and de -- so they looked at the patents -- and deformulation results of the -- in other words, they took ours, they deformulated it, and they copied it.

In fact, they say, brimonidine .15 percent, the strategy, develop identical to the listed drug, Alphagan P. And they did, and that's why they have stipulated that they infringe.

Who else has recognized that what we have done is new, novel and inventive. The FDA. Remember their skepticism back in 2003?

Now we are up to 2007. Alphagan P has been on the market. Physicians have voted with their feet on this one. They are going with Alphagan P for all the reasons I have told Your Honor. Exela decides, all right, we don't want to infringe. We are going to design around. And the way we are going to design around is we are going to make Alphagan again, except that won't do us any good because if we simply make Alphagan all over again, then we are already behind five, six other generics that are out there on the market. Alcon is already out there with a generic Alphagan.

Bausch & Lomb is out there with a generic Alphagan. As we can see, combined, they are only getting ten percent of the market. So Exela says, what we will do is make the original Alphagan but we will make it look like Alphagan P by reducing the amount of active ingredient to .15 percent. That was going to be their formulation. They said to the FDA, here is what -- here is our generic version of Alphagan P. Look. All we have to show you is biological equivalence, and the brimonidine in Alphagan P is at .15 percent, and our brimonidine is at .15 percent, and that's good enough. Right? Even though our pH is significantly lower, even though our preservative, this BAK, which was in the original Alphagan, not Purite, even though essentially everything about this is the original Alphagan, because we have lowered the brimonidine to .15 percent, that is going to be a generic Alphagan P.

Now the FDA, four years later, is saying, no way. That's absolutely not. Why not? Because, this is the FDA, in June of 2007, to Exela: Exela, there is evidence that pH and/or Purite preservative plays a role in the ocular bioavailability of brimonidine. They may not have gotten it in 2003, but even the FDA can reconsider, and now we have seen it, there is evidence that there is a lot more going on here than we thought.

Exela, the current reference listed drug --

that's us, Alphagan P product -- Alphagan P .15 percent solution with Purite as a preservative has the pH range of 6.6 to 7.4, whereas the test product, yours, Exela, with BAK, benzene alconium chloride as a preservative, has a pH range of 5.5 to 6.7.

You, Exela, have not shown conclusively that the difference in pH range between the test and reference listed drug products has no significant impact on the bioavailability or efficacy of the drug.

Exela, no. And they told them, you got to go back to the drawing board, you got to correct it. As Your Honor will see, they didn't, and the FDA has now closed their ANDA.

So we are not exactly sure what case we are trying here against Exela. But we are here, and Exela is here. So you move ahead. And we need to show that Exela's product that they may eventually get FDA approval on, if they go back to the drawing board and change their ANDA, will, indeed, have to be infringing. And why?

Well, first of all, let me say this. Exela has stipulated, or is not arguing, that they don't meet all of the elements of the '834 patent except for one thing, and the one thing they are arguing about is their pH. They are saying, we are below 7.0. We are not about 7.0 or higher, we are below 7. That's why we don't infringe the '834

patent.

The problem is that Exela's own internal data shows that in order to hit even their target pH, at some point they are going to have to make an infringing product.

And, of course, the patent laws say, it isn't just the using and the selling, it's the making. And it is our contention, Your Honor, and our expert will so testify, from Exela's own internal documents, that in order to hit even their target pH, because of this drift that I told you about, the pH drift, they are going to have to start with a formulation that is about 7.0 or higher. How do we know that?

Their target pH is, well, they keep changing it, but we think it's around 6.5, between 6.3 to 6.5 -- 6.5 to 6.7, I am sorry. Exela's own internal data shows that when they start with a pH of about 6.7, in about three months time, at this size bottle, it has dropped all the way down to 6.2. When they start out with a pH of 6.7 with this size bottle, it's dropped all the way to 6.4. And at three months with this size, it's dropped to 6.5. In other words, all of their pH's, all of these formulations have significant pH drift.

What does that mean?

They did accelerate a study, where they said, let's accelerate the formulation and see whether or not what

happens when you accelerate and the pH drift rather than over three months time, they did this from zero to three months, rather than the previous one that went out to six months. And what does it show?

Once again, it shows a drop all the way, being accelerated from 6.7 all the way down 6.2. What does that mean? What it means is this. This is again an Exela internal document. They did studies in India, Your Honor, on the pH, also. And what they did was they saw that if they are going to end up in their target pH of 6.5 to 6.7, which we admit is not about 7.0, if they are going to end up there, look where they have to start, Your Honor. They have to start right here, 7.1.

So in order for them to hit their target range, they have he infringe. They have no choice. They will begin with a pH of about 7.0 or higher, even to get down to their lower pH.

And that is the infringement case against Exela.

So I have now gone through four of the five patents. There is one left to go. That is the Purite patent.

What happened, Your Honor, is that long before the formulators came up with the invention that would become Alphagan P, there was a company called Bio-Cide. And Bio-Cide had a product which they called all sorts of

things. It was an interesting company. They called their product Purogene.

Sometimes. They called it Oxine sometimes. They had terrific salesmen. The salesmen would go around and say, you can use our product to fog your hog barns, literally. I never heard of it before. It's hog fogging. It is a way to disinfect a hog barn, you fog it, you take this Purogene and put the fog in and, poof, it disintegrates the hog barn. You can clean bed pans with it. Clean, I think, mortuaries with it. They had all sorts of uses. Short of suggesting you wear it as a hat, they were telling any company that would listen, you should try this, as a disinfectant, or even as a preservative.

THE COURT: Sounds like Listerine or something.

MS. BROOKS: Interestingly, it is almost because this is a label off of this Purogene, one of their Purogene products called Oxine. This is right off their product: "Caution, keep out of reach of children. Harmful if swallowed. May cause irritation. Avoid contact with eyes.

"Active ingredient: Chlorine dioxide."

They came to Allergan and said, why don't you put this in your ophthalmic products?

Now, you can imagine the reaction that these salesmen got from Allergan when he suggested that. However, to our inventors' credit, and these are different inventors

now, you will hear from Mr. Dziabo, they thought, all right, we don't think we can do what you are suggesting. But maybe there is something here that we can work with, and if we work hard enough, maybe we can come up with something that will be new and novel and different than simply taking what you are suggesting and putting it in an ophthalmic medication.

And so what they discovered was that -- what Bio-Cide was selling was this idea that if you took something called sodium chloride and you were able to release from it chlorine dioxide, and that was the Oxine label we saw right here, this chlorine dioxide, that that, the chlorine dioxide, is what you could use as your disinfectant or your preservative.

Now, there were lots of problems with that. One of the problems is the chlorine dioxide is extremely -- first of all, you are not supposed to put it in your eye. Secondly, it is extremely difficult to work with. It can turn into a very volatile gas and actually explode.

So there were certainly problems with that. But Allergan had been working with other gaseous antimicrobial agents. So they thought, well, there is something interesting here. We are not going to do what you are suggesting, no, but there is something interesting here and maybe if we work with it a little bit more we can figure it

out.

And here is what they figured out. They figured out that if you take the sodium chloride, don't turn it into the chlorine dioxide, but simply keep it as the sodium chloride, and if you use it in exceedingly small amounts, in a certain way, guess what? You can use it as a preservative. And that, in fact, was awarded a patent by the United States Patent and Trademark Office, the '078 patent. Aqueous Ophthalmic Formulations and Methods for Preserving Same.

Your Honor, the '078 patent was based on the fact that until Allergan figured this out through their own internal testing, it had never been done. There were preservatives out there. And, in fact, the most common one was benzene alconium chloride, or BAK, I will call it, used in many, many ophthalmics, still used in many ophthalmics to this day.

Purite, however, brought the benefit that once it is put into the eye, actually turns into a completely natural product of the eye. So it is a gentler preservative. It is much more easily -- who would have thought that from fogging your hog barn through the work of Allergan you would get this gentle preservative?

But they did. And as a result, they got the '078 patent. And it was only after they did testing

internally at Allergan, tried these different ways of getting there, that finally they saw that their formulation results met the U.S. PET criteria for preservatives.

I don't want to leave out that second part, because I don't want to look like I am trying to be misleading.

Allergan had even more stringent internal criteria, particularly for Europe, they had certain requirements for Europe dealing with this particular kind of microbial preservative. And it didn't meet that particular criteria. But it did meet the U.S. PET criteria for preservatives, and therefore it was approved as a preservative in ophthalmics.

So just so we are clear, Your Honor, because there is going to be a lot of misnomers, what the defendants will call stabilized chlorine dioxide -- and actually the industry calls it stabilized chlorine dioxide -- isn't chloride dioxide at all. What you are putting in your eye isn't that chlorine dioxide off the label that has the big "Don't put this in your eye."

What Allergan developed, invented, and discovered is actually chloride. And the chloride is both safe, it's stable, and it kills the microbes and the microbials very slowly. That's why it acts as a preservative rather than a disinfectant that goes in there

and goes, kaboom, your hog barn is now disinfected. The chlorine dioxide on the other hand is explosive. It also evaporates so it is not going to work very well as a preservative because a preservative has to stay in solution and act as a preservative throughout time. Of course, it also kills very rapidly, which is not, again, something that is particular good for the eye.

And that, Your Honor, is the story of Alphagan P.

It took me quite a while to go through because it took the inventors quite a while to accomplish. But as a result, we have these five patents before Your Honor, and we have generics switching to copy our formulation and Allergan wishing to protect its patent rights. Thank you.

THE COURT: Thank you, Ms. Brooks.

Do the defendants want to preserve or do you want to open now?

MR. BOGGS: I would like to open now.

MR. BREISBLATT: Your Honor, we will open as well after Mr. Boggs.

THE COURT: Let's see where we are.

MR. BOGGS: Thank you, Your Honor.

Your Honor, Exela is here today to clear a hurdle necessary to proceed with its .15 brimonidine tartrate formulation. I want to make it clear through our

words and the evidence that we present at this trial that Exela wants to market its own generic but noninfringing formulation. That's Exela's point. That's its theme. That's what Exela is all about, its own formulation.

The evidence we will present will show that Exela is a pharmaceutical formulation development company. I underscore the words "formulation and development." Exela does different formulations. The evidence will show, and I think Allergan has already alluded to the fact, Exela is not seeking to market a copy of Alphagan P, the brand name drug. And Exela has gone to great lengths to formulate its product to avoid the legal scope of every patent that Allergan says covers the product.

The testimony will be that approach is Exela's business model. It is a reformulation company.

Exela believes that it can safely reformulate drugs by changing things like preservatives, like buffers, like viscosity enhancers, like the specifications, and avoid patent infringement claims.

They can have their drug. But we can have ours, too.

It's that approach that is why we have not been sued on five patents.

And it's that approach that is why we haven't even been sued on all the claims of the '834 patent.

The idea underlying Exela is that they can reformulate, avoid infringement, avoid these types of lawsuits, and avoid the 30-month stay that is associated with Paragraph 4 litigation. And, then, they can get lower cost generics to those that need them even faster than the ordinary course.

The whole idea is not to get sued. They can have their patents, they can have their products. Exela wants to compete with them fair and square in the marketplace, with a different but bioequivalent and noninfringing formulation.

The evidence will show that Exela's formulation will contain .15 percent brimonidine tartrate. But the similarities with Alphagan P pretty much end there. The Exela formulation does not include carboxymethylcellulose slows as a thickening agent. More importantly, a solubility enhancing component.

We have no solubility enhancing component. It will not contain Purite as a preservative. It will not have a borate buffer. And it will not have a pH of 7.2.

The testimony will be that it's not just the .15 percent brimonidine that makes Alphagan P the product that it is. It's the combination of all its excipients together, which make up that product which people on the market know.

This, we will see, is an important conclusion to reach in this case when we decide whether the '834 patent claims are truly a fair characterization of Alphagan.

Why is that important? Because Allergan will attempt to attribute the product's success and unexpected results associated with Alphagan P over the entire scope of the patent claims of the '834 patent.

Next slide.

This is a demonstrative here, but it says it best. This is like attributing the characteristics of one solar system or the terrain and the atmosphere of one planet to every planet in every solar system in the entire Milky Way. I heard that the claims of the '834 patent are very narrow. If they were very narrow, we wouldn't be here, where we are today in this courtroom.

They are not narrow. They are not even close to being narrow.

The testimony will show that the Exela product will have a formulation much more like that of Allergan's original Alphagan product, the original Alphagan product was not patent protected. And long ago, original Alphagan was pulled from the market and abandoned by Allergan.

The testimony will be that like original Alphagan, the Exela product will contain polyvinyl alcohol as a viscosity enhancer. The testimony will be that like

original Alphagan, the Exela product will contain benzyl alconium chloride, or BAK, as the preservative. And the testimony will be that like original Alphagan, the Exela product will contain a citrate buffer.

The evidence will also show that the labeling pH of the Exela product will be 5.5 to 6.7, which embraces completely and entirely the labeling of 5.6 to 6.6 of Alphagan.

Obviously, with such vast differences between these two products, the question arises: How can Exela's product possibly infringe a patent on Alphagan P?

Well, it doesn't. And Allergan is overreaching. The testimony will be that there is no infringement of the '834 patent.

Allergan is looking at experimental products, exploratory experiments, and speculative, hypothetical FDA approval for which is not being sought to prove their case.

All of those experiments, exploratory experiments, would be unlawful if marketed. They are entirely irrelevant to this case.

All of the claims of the '834 patent require a pH of about 7.0 or greater. They also require that the brimonidine be soluble in the composition at about 21 degrees C. The evidence will show that the specification for the Exela product for which it seeks approval will

require, in all cases, a pH of 6.7 or less.

And that is true whether or not it's the manufacturing pH, 6.5 to 6.7. That is true whether or not it is the release pH, 6.2 to 6.7. And whether or not it's the shelf-life pH, or the stability pH, which is 5.5 to 6.7.

I expect that we will hear Allergan's own expert, Dr. Stella, testify that a pH of 6.7 is not a pH of about 7.0 or greater. And there is a well-settled scientific reason for this. It is not a question of semantics. The testimony will be that a brimonidine formulation with a pH of 6.7 will be much different than one with a pH of 7.0.

The evidence will be that pH affects dramatically both the solubility and the amount of unionized brimonidine that is available to treat the disease of glaucoma.

THE COURT: I am sorry to interrupt. Isn't that -- there is no dispute over that, is there? I thought I heard that point you have just made is agreed to.

MR. BOGGS: They have never stipulated that our formulation --

THE COURT: That is that 6.7 is not 7.0.

MR. BOGGS: That's correct.

THE COURT: Is that something over which there is a contest?

MS. BROOKS: No, Your Honor.

THE COURT: I just wanted to make sure. Perhaps we don't need to spend time, testimonial time, jousting about that.

MR. BOGGS: Okay.

So it affects both the concentration of the unionized brimonidine as well as the solubility profile of the two products. They are different. I will move on to another section.

As I mentioned before, Your Honor, it's not Exela's objective to get sued. The way it's supposed to work is that Exela notifies the brand name company of what it's doing and then the brand name company considers that information and agrees that it doesn't infringe, and then once Exela gets product approval from the FDA, they can get that medicine to the people that need it much quicker. They don't have the 30-month stay. They don't have this. They can go right there.

However, should Exela get sued, like it has here, it will raise the defenses that are available to it. And it has done so here.

The evidence will be that the Alphagan P was a straight reformulation of original Alphagan. Alphagan P resulted from the application of known design options, predictable solutions, and anticipated success. All driven

by the design need for market pressure to reformulate original Alphagan.

Alphagan P was not a product of innovation. It was a product of ordinary skill and common sense.

It was obvious, and it was unpatentable.

One of the things that is at play here is the Henderson-Hasselbach equation, which is pretty standard science. What the Henderson-Hasselbalch equation is, and Ms. Brooks indicated it before, the closer you get to the pKa of these salts, like brimonidine tartrate, the more -- the more unionized species that you have will be available.

The testimony will show that when it decided to reformulate original Alphagan, Allergan used a very similar approach to Dr. Koneru, the one that he used in order to reformulate the product, which came to be known as Alphagan P.

The testimony will be that Allergan substituted known preservatives and known buffers and known viscosity enhancers to get exactly the result one of ordinary skill in the art would expect, starting with the commercial product, Alphagan, it substituted a known preservative, which was the Purite. It substituted a known viscosity enhancer for that used in Alphagan, and the testimony will show that Allergan then made the expected and routine adjustments in concentration and pH that one of ordinary skill in the art

would do to accommodate those changes. There were no unexpected results. There were no unexpected advantages. And there was no surprise.

It was a routine reformulation, one that was well within the ordinary skill in the art.

Alphagan P is a nice product, it's a good product. But in terms of scientific advancement, it is no penicillin and it is no polio vaccine.

So let's look at it a little bit more closely.

The evidence will show that in 1996, Alphagan, the original Alphagan, was a soluble therapeutically effective and commercially successful ophthalmic formulation. It had a pH of 5.6 to 6.6. Original Alphagan contained .2 percent brimonidine, BAK, benzene alconium chloride, as a preservative, polyvinyl alcohol as the viscosity enhancing agent, and a citrate buffer.

Allergan's testimony will be that Allergan wanted to reformulate Alphagan to reduce its adverse effects. We can debate that, but we don't need to.

We can accept that, and that would be the design need or market pressure. In particular, the testimony will be that Alphagan irritated the eyes. They have different names for this. It comes in all different forms. They call it red eye, allergy, allergic conjunctivitis, we saw that, discomfort or just plain old-fashioned irritation.

And another problem with Alphagan was its sedative effect, sedation, it caused drowsiness. That is in the file history. That is in the literature. We heard about it before I was here.

Now, we will see that benzene alconium chloride, or BAK, which is the preservative used in almost all eyedrops worldwide, is notorious, notorious, for irritating patients' eyes. Now this would be the known cause of the problem, the known cause of the problem. And we will see that Allergan chose to substitute the gentler Purite, also a known preservative for eye drops, and it's known to be gentler. That would be the application of a known design option to solve the problem.

In fact, the evidence will show that Allergan, itself, as I said, had an eyedrop on the market using Purite as a preservative, that was the Refresh Tears we heard about. And I have heard it described as Allergan's flagship, flagship eyedrop product. They knew all about it.

This would be the predictable solution and the anticipated success associated with dealing with the irritation caused by BAK.

The evidence will show that the decision to change the preservative, that decision, change the preservative, then led to some additional but routine and expected formulation adjustments. In other words, ordinary

skill and common sense.

Whenever you change anything, you have to tweak it a little bit. The evidence will show that it was known that Purite requires a pH of neutral or higher if you are going to use it in a formulation. It degrades at pH's lower than that. So the pH of the formulation was increased. That's a predictable solution, anticipated success.

The evidence will show that it was known that at the chosen pH of 7.2, citrate buffers aren't useful at that pH. But borate buffers are. There is no magic here. Predictable solution, anticipated success.

What about reducing the concentration of brimonidine? What about that? It is important, or so it seems. But that is the biggest fiction of them all. The evidence will show that the increase in pH required a reduction in the concentration of brimonidine. It required it.

That was no unexpected advantage, as I frequently hear. It was required. What do I mean by that?

Remember the sedative effect of brimonidine, the sedation? That was an adverse effect. When you raise the pH, you increase the amount of brimonidine that's going into the eye, that is transporting across that eye membrane. If you are going to raise that pH, you don't want to put more of that stuff in there. You are going to aggravate that

sedative effect. And that was a serious side effect.

So how do you deal with that? You just lower the concentration. You just lower it. That was required. That wasn't an advantage.

I expect the Court will hear from Allergan's own expert that everyone knew, everyone knew, that raising the pH of amine drugs, including alpha-2-adrenergic agonists, such as brimonidine, increases the amount of unionized form and thus their bioavailability.

You want to raise the pH to get better bioavailability. That's taught by every paper of amine drugs. So if you know you are going to be dumping more brimonidine into the body and you know that it causes a sedative effect, you need to reduce the amount.

Much will be said about the advantages of Alphagan, but that's only meaningful in a legal sense if the advantages or results would have been unexpected, unexpected to one of ordinary skill in the art. And nothing like that, nothing like that exists here. The evidence will show that it was not unexpected that changing the amount of brimonidine from .2 percent to .15 percent would provide a therapeutically effective drug.

As I said before, on this slide, everyone knew that it was known that raising the pH increases the bioavailability. That is the Henderson-Hasselbalch

equation. The Henderson-Hasselbalch equation is basic, standard chemistry. It's a hundred years old.

If you have an amine drug, you want to raise the pH to get better bioavailability. That is taught by every paper of amine drugs.

Now, the evidence will show that the means existed to predict the result. The means existed. It was in the literature. You will hear about the Walters' paper. The Walters' paper reports on results from clinical trials associated with the original Alphagan product. And this graph here comes right out of -- it is Figure 3 in the Walters' paper. And it shows the therapeutic effectiveness of a .08 percent solution, a .2 percent solution, and a .5 percent solution.

Completely surrounds, completely surrounds .15.

Now, I think you could predict, and that's what that red line is, you can predict therapeutic effectiveness with .15. It's right there. It's within the error bars between .08 and .2. There was no surprise that .15 was therapeutically effective.

Now, this is a blockbuster. Contrary to what was said during prosecution of the '834 patent, and contrary to what we have heard, the evidence will show that it was not unexpected that one could raise the pH to 7.0 or greater to a soluble .15 percent formulation of brimonidine

tartrate.

The problem here with this '834 patent and what we are looking at is this lower limit of 7.0. What they say about solubility and the difficulties with solubility may be true at 7.5, where you need these magic solubility enhancing components. But not at 7.0. Exela does not use a solubility enhancing component. That's what their invention is all about. And it's all about at 7.5.

But what does this chart show, and where did it come from?

Well, Allergan, itself, disclosed the solubility profile for brimonidine tartrate when it filed its NDA in 1996 on the .5 percent formulation of Alphagan. This is a publicly available document at the FDA. And what this shows, and we have highlighted it, pH 7.0, you can be soluble all the way up to .194 percent. That is more than .15. Less brimonidine, anything less than that, than .194, will be soluble at a 7.0.

It was no surprise that at 7.0, a .15 percent solution could be made. But that's the cornerstone, that's the cornerstone of their nonobviousness case. And, you know, that may be true if that claim started at 7.5. Up here on this chart, 7.5-80, .15 would not be soluble at 7.5. But all this information was available, you can get it through a FOIA request, we did that.

Now, I heard a story this morning, and there is a lot of evidence to look at. And the evidence will show that we can endlessly debate what Allergan's true motives for immediately setting out to reformulate the commercially successful Alphagan was. And we can endlessly debate what the problems that they were trying to solve were. But we don't have to do that here. We can use Allergan's own spin in this case, and at the end of the day, the legally relevant motivations existed to do what the Allergan scientists did, regardless of their motives for doing so. It was a routine reformulation of original Alphagan.

Of course, when Dr. Koneru set out to formulate his product, he had one issue to address that Allergan didn't. And that's these five patents that we are talking about in this lawsuit. Now, Dr. Koneru had to formulate his product with an eye towards the claims of all five of those patents. Now, today, there is no dispute with respect to four of them, and it seems that there is no dispute on infringement with respect to the fifth.

But the evidence will show that when he was designing his formulation and looking at the '834 patent, that Dr. Koneru observed that it's not clear what the boundaries of the '834 patent claims are, or even when it was filed, if the '834 patent was intended to cover what they finally claimed.

Now, these are series flaws. These are series flaws. Lack of written description, lack of enablement, and indefiniteness, they all come to mind.

Those are just some technical problems that people kind of dismiss. Is it really a problem that the boundaries are unclear in these claims? Well, yes, it is.

The claims serve a necessary and important notice function to competitors and the public, like Dr. Koneru, and the requirements for claims are statutorily defined in 112. The public is entitled to know where the boundaries of claims are. That is a fundamental principle of the patent system. Allowing others to freely operate, just outside the bounds, like Dr. Koneru, that encourages innovation. Dr. Koneru's work in its way is innovation. He is working outside the bounds.

Now, with the claims that we will see -- and we will look at them much more closely through the course of this trial -- with these claims with uncertain boundaries, that stifles innovation. People are afraid of it. But it is the patentee's responsibility to make sure, when they draft their claims, that the public will be able to understand what they mean. That's the bargain they strike with the government when they seek their monopoly.

I want to look at two ranges that we see in the claims of the '834 patent. The first one is "up to about

0.15 percent."

The other range is a "pH of about 7.0 or greater."

There is that 7.0. 7.0, that doesn't mean an SEC.

I talked about that earlier. But let's look at up to about 0.15 percent. What does that mean? Where did it come from? What's the lower limit of that?

We know the upper limit is about .15. Well, the evidence will show that that range came out of the blue, just completely out of the blue. There is no disclosure of the lower limit of that range. That range was not in the specification as filed.

Now, with regard to the lower limit, it is impossible, impossible to determine what it is, because its meaning depends on another phrase that's in the claims, and that is therapeutically effective. You have to know what that means before you can determine of what the lower limit of "up to about .15 percent" is.

Now, people will say, will, therapeutically effective, that is effective for glaucoma. That's effective for reducing intraocular pressure. Well, I don't know the degree to which you are going to do that, but there is not a single mention, not a single one, of glaucoma or intraocular pressure in the '834 patent. And I suspect that's true with

the other three patents as well. Not a single mention. I saw pictures of glaucoma. I was talking about how it works. And there is no doubt in my mind that Alphagan was used to treat glaucoma and so on and so forth. That is not mentioned in these patents, in the specification.

That's why I asked the question, it's not clear what the patent applications were intended to cover when they were filed, but after they were pending for a while, all of a sudden, up to about .15 percent comes in, brimonidine tartrate comes in. And now it's covering a treatment for glaucoma and it's Alphagan P.

But we will look, at this trial, at the progression of the prosecution and we will see how this evolved.

Now, with respect to the lower limit of this claim, I expect Allergan's expert to testify as he did during his deposition, that, at some point, as you move down the range of .15 percent, you reduce the concentration, you are no longer going to have a concentration of drug that is effective.

That is common sense. However, I learned, it's not predictable where that point is. It requires a value judgment. It is often based on animal studies. And then you take that data, I learned, you take that animal study data, and you hope that it will translate into humans. We

saw an internal document today from Allergan where they said it was a failure, that because their data did not translate from the animal studies to the human studies, that is exactly what we are talking about here. And then, once you have gone far enough to do that, going to humans is limited, doing human clinical trials is limited, because of costs and because of the things you can do to humans at clinical trials.

It was described to me as a dilemma.

So where do you draw the line? What is the lower limit of up to about 0.15 percent? You have to do clinical trials to figure it out. Is that a problem?

Yes. It's a very big problem. The claims as written are broader than their neighbor link disclosure. The specification must teach those skilled in the art how to make the full scope of the claim, not Alphagan P at .15. And you have to make that teaching, it has to be the full scope of the claim without undue experimentation.

Animal studies, hoping that they translate into human studies, human clinical trials, I think that's undue experimentation.

Now, I said before, up to about 0.15 percent just appeared in an amendment. It appeared. There is a lack of written description for this range. It is a range. There is a whole body of law on ranges. You have to

disclose the invention when you file your patent application. Not at some point later. That's what happened here. The test, of course, is whether the specification indicates that the inventors were in possession of the invention as later claimed. This is new matter.

The specification didn't mention this range. They will point to little data points and charts and try to cobble together this range. This range, they were not in possession of this, or they concealed it when they filed their patent application.

And, as I said before, that patent application makes no mention of glaucoma and IOP, intraocular pressure. You couple all that with the fact that there is tons of unpredictable experimentation that would be required to know what the lower limit of this claim is, the inventors were not in possession of this range when they filed their patent application.

To this day, no one is in full possession of this range. No one knows what the lower limit of that is.

Now, the other range I want to talk about is pH of about 7.0 or greater. All the same problems exist with this one as well. The testimony will be that this range was not in the original specification or claims, neither one, it wasn't in the original specification, it wasn't in the original claims.

You may remember from the Markman hearing what is in the specification is 7, but not 7.0. And we discussed that at great length in terms of construing the claim.

But what is the upper limit of this? The pH range goes to 14. I saw a chart this morning that went to 10. Dr. Stella, Allergan's expert, told me the upper limit is 8.5.

Now, we also heard this morning that, depending on where you are in that scale, a solubility enhancing component is required. I think it's around 7.4 or 7.5. The claims in the '834 patent do not require a solubility enhancing component. They have a pH that can go up to, depending on who you talk to, 8.5, or 10, or 14, which is the end of the pH scale.

How do you make a soluble brimonidine tartrate formulation without a solubility enhancing component at a pH of 11 or 12 or 13? These claims encompass such things, but they are broader than the enabling disclosure. They encompass inoperable embodiments.

The specification does not teach those skilled in the art how to make and use the full scope of the claims without undue experimentation.

Now, we have come full circle, and you have heard me ask the question at the Markman hearing, Where do you draw the line? I have asked it several times today:

Where do you draw the line?

The bottom line, although it seems to be solved, they have drawn the line. They have said 6.7 does not infringe. So we are okay.

But the real answer is, none of us should be in this position where we are guessing what about 7.0 or greater is. And almost by definition, that impinges on another part of the statute, which is the second paragraph of 112. The claims are vague and indefinite. We don't know the metes and bounds. That's a problem.

Now, to wrap it up, at that point in time when all the evidence is in, at that point in time, and the smoke begins to clear from all of these validity challenges and the witnesses and the testimony, there will be the one fact that remains about Exela, and it will remain unchanged. Exela will still be seeking FDA approval for one and only one formulation. That formulation is the one set forth in the Exela ANDA. By FDA specification, that formulation has a pH that never exceeds 6.7. And that's all that's important. That's all that matters here. And that's the one piece of information that you need to decide the one issue, which is the cornerstone of the Exela business model, which is noninfringement.

This case is not about all the distracting flack to Exela. Prior experimental formulations, they are not

relevant. Prior exploratory experiments in India, they are not important. And speculative, hypothetical formulation changes about moving pH to avoid stability problems, those are meaningless. The ANDA is what the ANDA is. Exela seeks FDA approval for one and only one product. And everyone seems to agree that it does not infringe.

Thank you.

THE COURT: Thank you, Mr. Boggs.

MR. BREISBLATT: Your Honor, do you exclude witnesses from the courtroom? Do you invoke the rule?

THE COURT: It's up to what counsel agree upon. I am comfortable with either. If you don't agree, I will invoke the rule.

(Recess taken.)

THE COURT: Counsel, please take your seats. We will hear from Apotex.

MR. BREISBLATT: Good morning, Your Honor.

THE COURT: Good morning, counsel.

MR. BREISBLATT: First of all, let me say that Apotex, the documents they showed you, yes, appear looked at other formulations. But once it realized that these patents, the five in issue were invalid, under the Hatch-Waxman statute, it did what it's allowed to do. It copied the formulation and it said, in its Paragraph 4 filing, which is the active infringement, that the patents

are invalid. So all that prior stuff just isn't relevant. But it's the kind of red herring that I think we will see a lot of in this case.

First of all, what does this case not involve? Well, it doesn't involve a new molecule. We have all heard how brimonidine tartrate was, in fact, in use at .20. It was being used to cure exactly what it cures. And there are no claims being made that somehow it is being put to a new use. The patents in issue basically cover a known formulation doing exactly what it was supposed to do, that is, relieve pressure on the inside of the eye and help treat glaucoma.

What it does involve is taking an artificial tears product, and why don't we go to DTX-10 at 59380. And this is an Allergan document.

THE COURT: Did you have anything you wanted me to have?

MR. BREISBLATT: No, because these are documents the Court will see later. What I want to hand up are two charts that are not in evidence. They are just demonstrative.

THE COURT: Okay.

MR. BREISBLATT: And to set the stage, if we look at this section here, and I will ask that it be pulled out, "Refresh Tears, which also contains Purite, is an

ophthalmic over-the-counter product for the symptomatic treatment of dry-eye disease."

That is important because one of the symptoms of glaucoma is dry eye. So people who are suffering from glaucoma, and they might have been taking Alphagan at this time, would have been using Refresh Tears. The other benefit of Refresh Tears is the FDA allows it to be sold over the counter. You don't need a prescription for it.

So all of the ingredients in the Refresh Tears are FDA approved, they are gentle on the eye, to one skilled in the art, it would have been a perfect vehicle.

Let me take a step back.

We heard a lot about what Allergan scientists did and what they tried and all that. Again, you read KSR, that is all irrelevant. What is relevant is what would one skilled in the art do before the filing date of the Allergan patents? So what we are looking at is in 1999, in July, one skilled in the art who would know these things, what would they do? And all that stuff about Allergan trying 20 inventions in 1995, 1996, we are just wasting the Court's time. It's just not relevant.

So what happens in July of 1999? Well, we know that Refresh Tears had been on the market since 1997, being sold and marketed in the U.S. and Canada. And what does it tell us about it? It has a large margin of safety for its

components, including Purite, including CMC, which we will talk about, and in clinical trials with Refresh Tears, there was no clinically significant findings in either safety or patient acceptability. It was perfect. It was a great product.

Let's go to Page 59381. Now, this is the background, the rationale for developing brimonidine Purite 0.15. Let's just look at why we would want to replace it. This is something that would be known to one skilled in the art. If we go down to -- down here, I will have that pulled out, "Brimonidine-Purite ophthalmic solution is a new formulation of brimonidine tartrate. The formulation differs from Alphagan in that it is preserved with a novel preservative, Purite, rather than benzylalconium chloride, BAK."

Now, you notice that is what Refresh Tears had -- it had Purite and CMC. Then it goes on to say, The replacement of BAK with Purite was initiated in an effort to improve the efficacy and/or tolerability of the Alphagan formulation.

Now, you will hear a lot of discussions about allergies and these percentages. But this tells us what the real intent was and it would have been obvious to anyone skilled in the art back in 1999, July of 1999, there was an understanding that BAK causes issues. And if we go down to

the next sentence, "Although BAK has been safely used in numerous ophthalmic preparations, it is known to induce corneal epithelial toxicity and cause allergic reactions in some patients."

There you have the motivation. One skilled in the art would have wanted to get rid of BAK with a former of brimonidine tartrate.

And, as we have already seen from a number of charts, one would have a goal to try and get a pH level of 7 or above because that's closer to the natural pH of the eye, again, something one skilled in the art would know.

Now, as far as Apotex is concerned, we challenged five patents. Our goal is to show that they are all invalid. We know we have a burden by clear and convincing evidence.

But the Supreme Court has made our job easier because of KSR, because it's done away with the teaching, motivation and suggestion. It's offered some other things. We can all debate it. Right?

But one of the things it does tell us is common sense is something that the Court can utilize. One skilled in the art can use common sense. As we have just shown, and why don't we put up DM-1, this is the chart I have to the right, that is all that went on here. They took a known glaucoma drug, which was brimonidine tartrate, they added it

to Refresh Tears, and it worked. It worked. No question about it.

Now, there has to be the minor adjustments for percentage. And percentage becomes kind of important. You will see in three of these patents, Allergan never tells us what the percentage of brimonidine tartrate is. It always just refers to it as therapeutically. A therapeutic amount. Well, we know everything above .08, .08 and above could be therapeutic. So to reduce the amount from .2, which was in their present product, to .15, one skilled in the art would try and do that. Why? It's logical. The less medication you give someone, the better it is. We are always trying to go to the lowest most effective dose. I think that was one of the charts put up by Exela's counsel.

At this point in time, meaning in July of 1999, that less effective dose was somewhere between .08 and .2. So .15 would have been a logical selection. As .1 is.

Now, for Apotex, we have been charged with infringing five patents. We are going to look at what I call the combination patents together. Those are the '873, the '210, the '337, and the '834. And they charge us with infringing 52 claims. We are turning out one product, one product, 52 claims.

How do you get 52 claims that cover a single product? As we will look, imaginative patent lawyering.

They had a good patent lawyer who used every word combination they could to describe the same thing.

If this Court finds that, in fact, it would have been obvious to combine brimonidine tartrate and Refresh Tears at a pH above 7.0, all those claims are invalid. All of them.

That is why we stipulated to infringement.

Now, there is something else that is interesting about these patents. Let me show you the front page of them. We will start with the '873.

I am going to highlight what it says. You shall find this on the front of each of the four patents in issue. Allergan's counsel didn't mention it. And I can understand why not. The Patent Office made Allergan take a terminal disclosure on each and every one of these patents. And they did it because the inventions were not patentably distinct. So they gave up any term of any of these patents that would be longer than the others, because they are all the same thing.

Now, what we have done to make it a little easier is we have prepared our chart No. 2. What this does is it takes the active ingredient, and the ingredient that they make all the claims about in these cases. And that's brimonidine tartrate, carboxymethylcellulose, which I will call CMC because I can't pronounce it right, and Purite.

And Purite is stabilized chlorine dioxide.

What they did, throughout the claims, is they gave them different names for the same thing. So instead of calling it brimonidine tartrate in every one of those claims, what they do is they refer to it as the therapeutically active component in some claims, the adrenergic antagonist in some claims, the alpha-2 agonist component in some claims, the quinoxaline component in some claims.

And I am not going to even try and explain the scientific terminology that comes after. But you know something? It's all brimonidine tartrate. In some cases, it might be broader and cover other drugs. But it all is brimonidine tartrate.

So, for example, why don't we pull up the claims of the '873 patent, just as an example. What I have done is I have taken by color coding system, and I just have now shown where brimonidine tartrate is, where the CMC is, and where the Purite is by color coding them. And what the Court sees is in all of these claims that Apotex has been charged with, it's just those three components. It's always the red, yellow and blue, brimonidine tartrate, it's Purite, and it's CMC.

Now, they could have saved us all time and just charged us with one claim in every one of these patents.

But I guess they thought if they charge us with a lot of them, it would look like we were really in there infringing to a high extent.

Bottom line: That's it. Brimonidine tartrate, Purite, CMC. And every so often, they throw in a pH greater than 7. And that's it.

Now, that's just the '873. Why don't we go to the claims of the '210.

Again, this patent adds a terminal disclaimer, and what do we see when we look at it? Red, blue, and yellow. And the reason why some only have yellow, you will see they are dependent claims. If you look at 23, it says, The composition of Claim 1. You look at Claim 1, there is a red and blue, red, blue and yellow.

Just because it's a dependent claim, you got to look back and say, What's it dependent to? And it will always be dependent to the red and the blue.

Why did the Patent Office allow it? Imaginative patent writing. You call it a different thing, it sounds different, even though it is all brimonidine tartrate. It's all different words. That is why I prepared the "also known as" chart. And that's how they got all those claims.

Let's move on. Let's look at the '337 patent.

Again, the red, yellow, and blue. Brimonidine, CMC, and Purite. And, remember, CMC was part of Refresh

Tears. It was there from the beginning. Anyone who added brimonidine tartrate to Refresh Tears would have gotten whatever effect there was from the CMC and the Purite and it would have been obvious to make that combination. You have the perfect vehicle. And it was all FDA approved.

Why don't we move to the '834 patent.

This one is interesting, because this is the one that Exela has been talking a lot about, so I am not going to dwell on it a lot. Here, they say, they don't claim, at least, a CMC. They don't even claim a solubility enhancing agent. But they do claim .15 percent, because at .15 percent, you don't need a solubility hang agent. Brimonidine tartrate is going to be soluble at pH's greater than 7. They don't claim it.

Of course, again, if you had simply mixed brimonidine tartrate and Refresh Tears, you would have had it. And one skilled in the art would have done that in July of 1999.

Now, just because Allergan didn't turn to it originally, we shouldn't reward them. Here is something that is very interesting. If you looked at the file history of each of the four patents we have just discussed, and they have admitted they took the Refresh Tears former and just put brimonidine tartrate in it, don't you think you should have told the Patent Office about Refresh Tears? They never

mentioned to the Patent Office, you look through every one of those specifications, you look through every one of those file histories, and they never told the Patent Office about Refresh Tears.

Not only that, and now we will get to the last patent issue, remember, they talked about the '078 patent and what a great invention it was because they took stabilized chlorine dioxide and they put it into an ophthalmic formulation? Don't you think they should have told the Patent Office about the '078 patent in the four patents we just looked at where they are claiming this preservative?

They don't mention it. You look at the face of those four patents, you won't see the '078 patent.

Now, the '078 patent claimed the use of the stabilized chlorine dioxide, which is the Purite, and, of course, it was invented by another company, and they make light of it. But why don't we put up the letter that was being sent out, PTX-216. And why don't we highlight -- yes. Now, this is a letter being sent out by Bio-Cide Chemical Company. It wasn't confidential. They just sent it out. They sent it out in 1983, which is years before, years before the patent was filed for in this case.

Bio-Cide is introducing themselves. They tell us that Purogen, which is the Purite, is a replacement for

your disinfectant Quadarine (phonetic), the paragraph above, and your preservative Dermasol. And those were preservatives in ophthalmic products.

So what Bio-Cide is telling Allergan and the public in 1983 is you can use our product. You can use our product as a preservative.

Now, there is another patent, and that's the '208 patent, JTX-071. Why don't we throw that up.

This patent is prior art. It is the Stokel patent. It was in front of the Patent Office. No question about it. But remember, again, this is prior to KSR, and the Patent Office rules have even changed since then. Why don't we go to the next page.

In this patent -- and we will go through it -- they talk about its use in ophthalmic preparation -- next page -- if I may have a moment, Your Honor.

If you go over to the summary of the invention, right after the first page, the second page, there we go, all right. Why don't we go to the '078 patent. I will come back to this, because it actually tells us what Stokel includes. If we go to the second page, this is the patent in issue, Your Honor.

They even can see, you see what it says about Stokel, it says, Stokel, et al., U.S. Patent No. 4,654,208 discloses an antimicrobial composition for contact lenses

including an aqueous solution of a germicidal polymeric nitrogen compound and an oxidizing agent, and it refers specifically to stabilized chlorine dioxide. And we will talk more about the Stokel patent as we go through. I apologize for that, Your Honor.

The use of stabilized chlorine dioxide in ophthalmic solution was known, that is the important thing. As the letter from Bio-Cide says it can be used as a preservative. So the earlier patent is invalid as well.

We believe, at the conclusion of the case, the Court will find that all that happened here was that prior art elements that were known were combined to yield predictable results. And that is the brimonidine tartrate and the Refresh Tears, as well as using the stabilized chlorine dioxide. The simple substitution of one known element for another to obtain predictable results -- again, they substituted a known ophthalmic vehicle without BAK to cure the BAK problem. The use of known techniques to improve similar devices, they used a higher pH to get better bioavailability, a well-known effect.

If we look at each of the factors that should be considered, we will find that all five of the patents in this case are obvious.

Thank you, Your Honor.

THE COURT: Thank you, counsel.

All right. Let's have our first witness. Have counsel agreed, or do I need to order sequestration?

MR. BREISBLATT: There has been no agreement between the parties.

THE COURT: Let's sequester the witnesses. To the extent there are experts in the room that need to remain, that's fine.

MR. BOGGS: Your Honor, Dr. Kuneru will be one of our witnesses. We have agreed that he can stay.

THE COURT: That is fine with the Court if the parties can agree.

MS. BROOKS: Your Honor, he can stay as Exela's corporate representative and he has signed under the protective order.

THE COURT: And I assume Apotex has no difficultly with that?

MR. BREISBLATT: We have no objection.

MS. BROOKS: Your Honor, our first witness will be Dr. Scott Witcup and Mr. Singer will be doing his direct examination. And he just needs a moment to set up.

THE COURT: Keep in mind, counsel, we will break at 12:30.

MR. SINGER: We will try to get through the whole examination before 12:30.

THE COURT: That would be great. That is not

what I was saying.

SCOTT WHITCUP, having been duly sworn as a witness, was examined and testified as follows.

DIRECT EXAMINATION

BY MR. SINGER:

Q. Good morning, Dr. Witcup. Thank you for coming today. Where are you currently employed?

A. I am currently employed at Allergan, Inc. in Irvine, California.

Q. What is your position there?

A. Currently, I am executive vice president and head of research and development.

Q. What does that mean your responsibilities are?

A. So all of the laboratory research and the clinical testing of our new treatments in patients is under my responsibility.

Q. How long have you been employed with Allergan?

A. I joined the company in January of 2000.

Q. Could you briefly describe for the Court your educational background?

A. Sure. I did my undergraduate work at Cornell University. I got a Bachelor's in biology in 1980. I then went to medical school at Cornell as well, as I was in New York City, completed that in 1984.

I then did two residencies -- after medical school, I went to do an internal medical residency at UCLA, and following that, did three years of ophthalmology training and ophthalmology residency training at Harvard Massachusetts Eye & Ear infirmary.

Following that, I went to the National Institute of Health and completed fellowship training in ocular immunology and uveitis, which is inflammation in the eyes, completed that in 1992.

Q. **Have you published in the field of ophthalmology?**

A. **Yes. I have a, over 150 published articles and the vast majority of those are in ophthalmology.**

Q. **Also, Dr. Whitcup, do you have any textbooks in the field as well?**

A. **I do. I co-author a textbook on inflammation in the eye on uveitis.**

Q. **Where were you employed before coming to Allergan?**

A. **Right before I came to Allergan -- after I finished my fellowship training at the NIH, I stayed on and I was clinical director for the National Alliance. So I ran all the intramural clinical programs for the government in ophthalmology.**

Q. **When you came to Allergan, what was your position at that time?**

A. **When I first came to Allergan, I was head of the**

ophthalmology therapeutic area. That meant in charge of clinical testing. So once treatments went into the clinic, human testing, clinical trials, those were under my responsibility.

Q. **Are you a formulation scientist or a clinician?**

A. **I am a clinician.**

Q. **What were your responsibilities in 2000 when you joined Allergan?**

A. **So we had a number of clinical programs. My responsibility was to make sure we were doing the right studies, ensure patient safety, help analyze those results, make sure that the studies were put together in new drug applications and interacted with the FDA to get treatments approved.**

Q. **About how frequently did you interact with the FDA?**

A. **It depended upon where in the cycle we were with various products. It could be daily. It could be once a week. There probably wasn't two or three where I didn't interact with FDA in some fashion.**

Q. **Did those responsibilities you had in 2000 include the development of new drugs?**

A. **Yes, it did.**

Q. **Also new glaucoma drugs?**

A. **Yes.**

Q. **And about how many products were you working on when**

you joined the company in 2000?

A. There were probably about ten or so major clinical programs going on when I came to Allergan.

Q. And about how many of them were glaucoma drugs that you took over?

A. There were probably about three that were glaucoma related.

Q. And have you, yourself, treated glaucoma patients?

A. Yes, I have.

Q. Do you still treat patients today?

A. I do.

Q. Okay. We have heard a lot about glaucoma. I want to give the Court a very brief background on what the disease is, a little beyond what Ms. Brooks said.

What is glaucoma?

A. As you heard, glaucoma is a disease where the optic nerve, the nerve in the back of the eye that takes vision from the retina to the brain, is impacted and actually dies. And as that nerve dies, patients lose vision, unfortunately.

Q. About how many people are affected by glaucoma in the United States?

A. We think over 3 million people in the U.S. have glaucoma.

Q. Is that a number that is going up or going down?

A. Unfortunately, it's going up, mostly because it's

associated with aging, so as the population ages, the amount of glaucoma is increasing.

Q. **I would like to put up a demonstrative. Did you bring one with you to help explain what happens when you get glaucoma?**

A. **Yes.**

Q. **If we could have ADX-2, the effects of glaucoma.**

Dr. Whitcup, Ms. Brooks explained a little of what we see here. I would like you to explain for the Court what is going on in each of the boxes we have here on the demonstrative?

A. **As you heard a little bit earlier this morning, patients with glaucoma first may notice changes in the periphery of their vision. So you can see, really, here, you see some blurring at the far periphery. One of the problems with glaucoma is actually some patients don't actually recognize that early change. We find that by the time patients are diagnosed, they have lost about 50 percent of that optic nerve.**

Q. **Just to be clear, the first is a patient with glaucoma or a patient about to get glaucoma?**

A. **That is already glaucoma. They have already had enough damage in that optic nerve that they have lost vision.**

Q. **Going to the intermediate box, what does that show?**

A. **Here you can see progression now, the loss of vision is moving more centrally. And the degree of the blurring peripherally is more severe.**

Q. **And then what is the layout box?**

A. **The layout box, actually, I have seen patients worse than this. Now the patient only has the central vision left. And with more progression of the disease, you can actually lose half of this. Unfortunately, some patients will lose all light perception, be able to see nothing at all.**

Q. **Thank you.**

Is there considered to be a primary cause of glaucoma?

A. **You know, the main pathological cause is pressure backup in the eye. We think that's the major risk factor for the disease. We think that that is due to the drainage system of the eye not functioning as well over time.**

Q. **Is there a normal pressure in the eye?**

A. **Studies show that the normal pressure in the eye is somewhere between 10 and 20.**

Q. **And the elevated intraocular pressure, what is that? Is it anything above 20?**

A. **It really depends on the patient. But typically, pressures of 22 millimeters of mercury, 24 millimeters of mercury or higher are then associated with high risk or**

higher risk of losing vision from glaucoma.

Q. **Did you bring a demonstrative to explain this effect as well?**

A. **Yes, I did.**

Q. **If we could have demonstrative Exhibit 3 on the screen.**

We saw this in opening, this graphic from the American Health Assistance Foundation. You talked about pressure. If you could describe for me, where is the pressure in the eye felt and what are we looking at?

A. **Again, a little bit hard to read on the chart, but the ciliary body, which is the structure where the arrow is pointing, is where the fluid in the eye is produced.**

Q. **What is that fluid?**

A. **That fluid is called the aqueous humor. The aqueous humor does a couple things. One, it keeps the eye's shape. The second important thing it does is it nourishes the cornea, the front part of the eye. It nourishes the lens. So it is a very important fluid in the eye.**

The problem is with glaucoma, as you can see in this bottom part, the fluid does not drain out of the eye as well as it should. So as the eye continues to increase fluid production, the pressure in the eye goes up, and as this diagram shows, that pressure from the front of the eye presses on the jelly in the back of the eye and then onto

the optic nerve. That pressure on the optic nerve causes the cells in that nerve to die.

Q. **Dr. Whitcup, why doesn't this fluid just drain out with our tears?**

A. **There is really no connection between tears and the fluid in the eye. The fluid in the eye actually drains out of the eye through the blood system, through the venous; it goes through a couple of pathways in the eye. But has nothing to do with tears.**

Q. **Thank you.**

Now, I want to go back to your time at Allergan and move forward. You talked about having about ten programs underway. Did you have a typical ratio of success when you have a program that goes into the clinic that you follow at your job?

A. **If you look across the industry, the statistics show that if you are lucky enough to get a treatment that the FDA allows you to go into humans with, you have got a one in eight chance of that making it all the way through clinical testing, filed with the FDA, and then approved.**

Q. **What is it that is filed with the FDA to gain approval?**

A. **So the documents that go into a New Drug Application, a whole host of information, from formulation work to animal testing to ensure safety, and then the vast array of the**

clinical studies that the FDA made require usually the Phase 1-2-3 studies you hear about.

Q. **There is a little jargon there. What is a New Drug Application?**

A. **A New Drug Application is the formal documents that the FDA requires to assess approval of a new treatment.**

Q. **Then you said Phase 1, Phase 2 and Phase 3. What is Phase 1?**

A. **Phase 1 is a clinical trial, it is the initial test in humans. It is usually done in normal volunteers. You usually start at a low dose of the drug and go up. It's usually about 40 to 60 patients on average. It's focused on safety. Really, is this drug safe at the doses you are testing?**

Q. **What is Phase 2?**

A. **Phase 2 expands on that safety testing, is a little larger in terms of the number of patients. Often, as opposed to the normal volunteers that you might do in a Phase 1, the Phase 2s actually now start testing patients with the disease. So you get your first hints of, Is the drug effective? So you said increased safety and some initial information on efficacy and the right dose that you want to pick. And these studies tend to be about 100 patients. So bigger than the Phase 1 trials.**

Q. **Then what is a phase three trial?**

A. **The Phase 3 trials tend to be the pivotal studies which the FDA bases approval on. They tend to be randomized trials, so patients either get the new treatment or control treatment or a placebo where they are randomly assigned to each of those treatment paradigms. They tend to be longer, up to about a year, and have many more patients. So typically a Phase 3 trial will be 600, 700 patients.**

Q. **All together, about how much time does all this take to put together?**

A. **We do some benchmarking. A typical -- the work that goes in to get to filing a new drug from start to finish is maybe somewhere between a hundred person-years, often 200 person-years.**

Q. **Did you bring -- is there an NDA example in the courtroom today?**

A. **Yes. I think we have the NDA for the Alphagan P .15 percent in the court.**

It was roughly 209 volumes, about 300 pages apiece. A lot of work goes into putting those together.

Q. **Is that a fairly typical size for the document?**

A. **It is typical, yes.**

MR. SINGER: Your Honor, we have identified that as Joint Exhibit 1. I would just move it into evidence, if you like.

THE COURT: It is admitted. It's already part

of the record.

MR. SINGER: Thank you, Your Honor.

BY MR. SINGER:

Q. A couple more background questions for our discussion.

Through your job, have you become familiar with the general FDA requirements for approval of an ophthalmic drug?

A. Yes.

Q. Recognizing it is a complex process, are there a couple touchstones that we can guide the Court with for FDA approval?

A. At the end of the evaluation, it always comes down to risk and benefit. Are the benefits of the drug treating the disease that you are addressing, do they outweigh the risks of the treatment that usually comes down to assessing both safety and efficacy?

Q. In your experience, what does "safety" mean?

A. So safety, especially when you are talking about eye medications, has two parts to it. One, how well tolerated is the medication for the eye, we have heard about some of the issues with the drug today brimonidine. But the drugs, once you put an eyedrop in the eye, will drain down your tearduct and get absorbed into the bloodstream. So there are systemic side effects with drugs as well.

When I look at ophthalmic medications, I assess

very carefully not only how well the eye tolerates the drug but what are the systemic side effects of that medication as well.

Q. **You used another term, "efficacy." What does efficacy mean in your experience?**

A. **Efficacy is how well the drug works, treating the disease that you are setting out to treat. In the case of glaucoma, the medications are indicated to lower intraocular pressure. So the FDA, after years of working on glaucoma medications, has very set ways when you measure the pressure, when you see the patient. So it is very standardized to establish what the effectiveness of that drug is.**

Q. **Have you also heard the term "line extension" in your work?**

A. **Yes, I have.**

Q. **What is your understanding of that?**

A. **Line extension is using the same active medication, so in the case of Alphagan, it was brimonidine, but using either a different concentration formulation, potentially a different indication. So something new for that active ingredient.**

Q. **And in your experience at Allergan, do line extensions result in improvements?**

A. **Absolutely. And that's always the goal as to**

improving. In fact, the group that worked on this is called product enhancement, product improvement. We really do want to make the product either more effective or safe.

Q. **Does the FDA apply the same standards to line extensions as it does to an original drug?**

A. **Yes. They, as well, want to make sure that the drug is effective and safe as labeled.**

Q. **In your job, how do you judge whether there has been an improvement made?**

A. **I look at the efficacy that comes out of the clinical trials. I look at the wealth of safety data that we have. It's my responsibility as the head of R&D to make sure our treatments are safe for patients. It is really my primary concern. I look at the data that goes into the New Drug Application. Then it really doesn't stop there. You want to make sure that once the product is approved, and patients are using it, is it safe out in the marketplace? The feedback that I get from my fellow ophthalmologists, saying that, yes, this is a better product and do we see that in terms of reported safety issues from our patients?**

Q. **I take it, from your testimony, Alphagan P is a line extension of Alphagan. Is that right?**

A. **That's correct.**

Q. **Do you believe it to be an improvement over Alphagan?**

A. **Absolutely.**

MR. BREISBLATT: Objection, Your Honor. Relevancy.

MR. SINGER: I would just add, if I could lay a little foundation, he is going to be discussing the clinical trials.

THE COURT: Okay.

BY MR. SINGER:

Q. **Dr. Whitcup, were you in charge of the clinical trials for the Alphagan P product?**

A. **Yes. When I came to Allergan, the Phase 3 studies were ongoing. But it then became my responsibility to make sure those trials got completed, helped with the analysis of the data, supervised putting together the New Drug Application.**

Q. **Was it your judgment that the clinical trials were suitable for submission to show an improvement over Alphagan at the FDA?**

A. **Yes.**

Q. **Based on that, do you believe that Alphagan P is an improvement over Alphagan?**

A. **Absolutely.**

MR. BREISBLATT: Objection, relevancy, and calls for an opinion outside -- he is not listed as an expert witness, Your Honor.

THE COURT: I wouldn't sustain it on the first

basis. But the second.

MR. SINGER: I can move on, Your Honor. That is perfectly fine.

THE COURT: Then I will sustain the objection.

BY MR. SINGER:

Q. Let's talk a little bit about the active ingredient and then go to the clinical trials that will be the subject of this case.

I think we heard that brimonidine is the active ingredient in both Alphagan and Alphagan P. Is that correct?

A. That's correct.

Q. How does brimonidine operate to treat glaucoma?

A. So brimonidine treats glaucoma by lowering the pressure in the eye and actually has two mechanisms of action to do so.

Q. About how much does brimonidine lower the intraocular pressure?

A. In the clinical trials that we have done, it lowers pressure by approximately five or six millimeters of mercury. As we said, the normal range is approximately 10 to 20.

THE COURT: What was the figure again?

THE WITNESS: About five to six.

BY MR. SINGER:

Q. **You said normal range is about 10 to 20?**

A. **Correct.**

Q. **Did you bring a demonstrative to explain the dual mechanism you have actually described?**

A. **Yes, we do have one.**

Q. **If I could pull up ADX-14, please, on the screen.**

This has a lot of arrows and some colors. What are we looking at, Dr. Whitcup?

A. **This is a cross-section of the eye. Just to orient the Court, this would be, for example, a patient lying on the back looking upwards. So the cornea, the front part of the eye would be toward the top, and that optic nerve that I talked about would be more toward the floor of the courtroom.**

This is the iris, the chloride part of the eye; here, this would be the pupil, just to orient you. This is the lens of the eye.

Q. **And there are a bunch of arrows, unfortunately, they are all the same color. What are the arrows showing?**

A. **This explains the normal flow and production of aqueous humor and then drainage out of the eye. Here is the ciliary body that we talked about before. That's the part of the eye that produces this aqueous humor or fluid in the eye. The normal flow of the fluid is to go into the front part of the eye through the pupil, and then normally drains**

out through two structures, not that the exact name matters, is called the trabecular meshwork and the other main pathway is the called the uveoscleral outflow pathway.

What this does is two things. One, it decreases the production of fluid, so it inhibits fluid production, and also increases the amount of fluid leaving the eye, and thereby lowering the pressure.

Q. **I think you mentioned earlier that there was cloggage in the drainage system in glaucoma patients. Where does that occur?**

A. **Typically, the cloggage, we think, occurs in the trabecular meshwork.**

Q. **Thank you, Dr. Whitcup.**

You talked about the clinical trials for Alphagan P that you were responsible for. I want to move to that.

When you joined Allergan in 2000 and took over the clinical trials for Alphagan P, what did you understand to be the goal of those clinical trials?

A. **The goal, we knew with brimonidine that there were several side effects that inhibited its use in patients. I had seen some of the side effects.**

One was the allergic conjunctivitis, the low tolerability what also concerned me was the systemic safety. So it was somnolence, which was an overall weakness, oral

dryness was another one that we watched for, because that was an indication, sort of a sentinel side effect that you were getting systemic absorption of the drug.

The systemic side effects were of concern because we knew, actually, if you give brimonidine, for example, to infants, we saw some infants stop breathing. This is not a subtle side effect. In older patients, we have done work to show that the amount of somnolence could be associated with severe car accidents.

Given that safety is a key concern, not only making the drug more tolerable to the eye, but decreasing the systemic side effects, were really critical components of the program.

Q. If I could just talk a minute about the local side effects you talked about, which I think you mentioned was the allergy. We saw the picture that was in opening statements. Is that the allergy that you are speaking about?

A. Yes. That's, you know, a case of allergic conjunctivitis that you can see.

Q. Can we have that demonstrative up, please?

What are we looking at here in terms of the effect of the drug on this person here, ADX-7?

A. Conjunctivitis basically means inflammation of the conjunctiva. The conjunctiva is sort of the white part of

the eye. That white part of the eye actually extends on the underneath part of the eyelid itself.

You can see on this patient, the eyes are very red, swollen, and the eyelids as well are involved with this inflammation. As noted before, just getting rid of bacteria would get rid of this problem. We didn't think that would at all make sense, because there are a number of medications. The leading glaucoma product, which is actually sold by another company, it Pfizer, called Salatin, has lots of BAK in it. And you almost never, maybe one in 1,000, would see this. And we were seeing this in 15 percent of our patients. We knew it wasn't a BAK problem. Maybe a gentler preservative may help. But this was due to brimonidine. And we knew that.

Q. **Is this a serious condition in your experience?**

A. **You can see, this patient is not a happy patient. They are calling up their ophthalmologist. So the ophthalmologist isn't happy. We talked a little bit in the opening statement as well, if you develop a sensitization like this to brimonidine, then you can't use it anymore. And although there are a number of other medications, brimonidine is used by a number of patients, and even with all the medications, there are still patients who don't get pressure lowered enough and you need then to go to the operating room.**

So it is an important motivation to try to decrease this type of sensitization so that people can stay on the medication.

Q. **Is the prognosis for a patient who has the allergy such that they can never receive the drug again?**

A. **Most ophthalmologists feel if you get an allergic conjunctivitis like this, you would not want to take a chance and re-challenge the patient to risk this a second time. So the vast majority of patients, once they develop this, they stay off the medication forever.**

Q. **You talked about systemic side effects as well. Just beg me some indulgence. You said A-S-T-H-E-N-I-A. What is asthenia?**

A. **Asthenia is a weakness, a feeling of over generalized weakness. That, in combination with somnolence, is the side effects that we knew occurred with brimonidine. We had seen it in a number of studies that we did so one we really wanted to try to reduce.**

Q. **What is somnolence again?**

A. **Somnolence is sleepiness. Again, we have done studies to show that the amount of somnolence you get with brimonidine with the .2 percent is severe enough to be associated with car accidents.**

Q. **Then, I think you mentioned one other, which was an oral dryness. What is the significance of oral dryness?**

A. **So oral dryness, as well as being a bothersome side effect that sometimes patients discontinue the medicine for, was important for us because you get it with systemic absorption of the drug.**

THE COURT: We are going to have to take a short break, counsel.

(Recess taken.)

THE COURT: Be seated. Sorry about that. Mr. Singer.

MR. SINGER: Thank you, Your Honor.

BY MR. SINGER:

Q. **I want to turn now from the side effects that you described to the clinical trials that you described you had responsibility for.**

How many clinical trials were done for the Alphagan P .15 percent project?

A. **I believe there were five total trials done, culminating in the two pivotal Phase 3 trials.**

Q. **What are the two pivotal Phase 3 studies again?**

A. **Those were randomized studies where we looked at the original Alphagan compared to two concentrations, .15 percent and .2 percent, in the Purite formulation with the changed pH.**

Q. **You should have a notebook up there. If you could turn in there to what's marked as PTX-367. Do you have**

that, sir?

A. **Yes, I do.**

Q. **Is that your signature on the face page of that document?**

A. **Yes, it is.**

Q. **Can you identify that document for the Court, please?**

A. **That is the final 12-month clinical study report for the first of the two Phase 3 trials.**

Q. **Was that submitted to the FDA in connection with the NDA for Alphagan P .15?**

A. **Yes, it was.**

Q. **If you would turn to the next document in your book, it should be PTX-417. Is that there, sir?**

A. **Yes, it is.**

Q. **Is that your signature on the face page of that document?**

A. **Yes.**

Q. **Can you identify that document for the Court?**

A. **This is the complete 12-month study report for the second Phase 3 clinical trial, Study 008.**

Q. **Was that also submitted to the FDA in connection with the study of Alphagan P 0.15 percent?**

A. **Yes.**

MR. SINGER: I would move PTX-617 and 417 into evidence.

THE COURT: Fine. These were pre-identified.

MR. SINGER: Yes, on plaintiff's list. They are a subpart of the NDA.

THE COURT: If these were all identified in the pretrial order submission, they are in the record.

MR. SINGER: Thank you. I won't take up the Court's time looking at documents then.

BY MR. SINGER:

Q. **Dr. Whitcup, as the person who signed off on these trials, what were the major results of these trials?**

A. **First one was efficacy, because we knew in talking to the FDA that there were very strict criteria to show that the pressure lowering of the new formulations was equivalent or comparable to the base Alphagan. We needed to have in statistical terms the upper limits of the 95 percent confidence intervals, which is a variability piece, within a millimeter at the majority of time points and within a millimeter and a half at every single time point. We measured I think at about 16 or 20 time points over the study.**

That was the key efficacy piece. And we showed that they were, in fact, comparable and did meet the FDA's strict criteria in each of the Phase 2 studies.

Q. **Was there a safety finding as well?**

A. **Yes. Importantly, we saw significantly less of this**

allergic conjunctivitis that we were hoping to see. And also we saw decreased systemic side effects, like the oral dryness, the somnolence and asthenia.

Q. **Is there a summary from which this data is put together?**

A. **The pooled data from those two Phase 3 trials was published in the Journal of Glaucoma subsequent to completing those studies.**

Q. **What is the Journal of Glaucoma?**

A. **The Journal of Glaucoma is one of the major peer-reviewed journals where articles focused on glaucoma are published.**

Q. **Who was that article authored by?**

A. **Dr. Jay Katz.**

Q. **Who is Dr. Katz?**

A. **Dr. Katz is a glaucoma specialist, who was also one of the investigators in the trial.**

Q. **Hopefully, you have that paper in front of you. It's EDTX-099. I know it's also in the pretrial order at DTX-17. Do you have that in front of you?**

A. **Yes, I do.**

Q. **If we could put that up on the screen.**

You describe, Dr. Whitcup, the general protocol of the study. Is there somewhere we can find that protocol?

A. **If you look, on the second page, under Study Design.**

Q. **If we go to the second page, please. Where do we see the protocol?**

A. **This basically describes the study design, that it was 12-month, it was double-masked. That means neither the patient or the evaluating physician knows. Actually, you may hear the term double-blind. In ophthalmology we don't use double-blind. Patients don't want to go into a study where they hear anything about blind. So we call them double-masked. But it's basically the same thing.**

The second paragraph talks about how the patients were randomly assigned to receive those three formulations of brimonidine, either the Purite formulation of .15 percent, the Purite formulation of .2, or the original brimonidine at .2 percent.

Q. **The original brimonidine .2 percent that we have highlighted, is that Alphagan?**

A. **That's correct.**

Q. **And is one of the other. 2 Alphagan P?**

A. **Yes, the .15 percent brimonidine Purite is Alphagan P.**

Q. **What was the purpose of studying both the .15 brimonidine Purite and the .2 brimonidine Purite?**

A. **To be honest, we were not sure that we would be able to maintain equivalent efficacy at the FDA's strict criteria with a .15 percent. We knew that systemically we would hope to see decreased systemic side effects by decreasing the**

concentration. But given the strict criteria, we weren't sure that .15 percent would meet the definition and may, in fact, not be equivalent. So we had the .2 percent in the Purite formulation study as well.

Q. **Does the paper report those equivalent results?**

A. **For the .15 percent, it does.**

Q. **And where is that?**

A. **That can be seen on the graph, I believe it's on Page 122, the manuscript.**

Q. **And which graph are you referring to?**

A. **It's on the bottom of the page.**

Q. **If we could blow that up?**

What are we seeing there on that graph?

A. **This summarizes the IOP data at just one of the time points.**

Again, we measured the intraocular pressure at multiple time points during the day. But for the article, just one of the time points was picked. You can see, the lines really do need to be right on top of each other to meet the FDA definition. This needed to be replicated at multiple time points in the day, at multiple study visits, in each of the two studies independently.

Q. **If there were a gap between the lines, what would that mean?**

A. **A gap, if you saw a gap on this, it would mean that**

you wouldn't meet the FDA's definition.

Q. **And you talked about the safety profile. Is that found in here somewhere as well?**

A. **There is a summary of some of the safety data, which is on the following page.**

Q. **Where are you referring to, sir?**

A. **If you go to the next page.**

The table at the top of the page. This summarizes some of the major findings of side effects, the top line is the allergic conjunctivitis. So you can see, it was 9.2 percent in the Alphagan P formulation. If you go to the far right, it was 15.7 percent in the Alphagan, and approximately the same, 14.6, in the .2 percent Purite formulation.

In fact, the .15 percent Purite was significantly less than either of the two other formulations. You can also then see oral dryness was significantly less than the original Alphagan. Redness of the conjunctival hyperemia was significantly less as was eye discharge.

Q. **In terms of patients, we have had a lot of numbers thrown around right now, what is the difference between the 15.7 percent allergic conjunctivitis and the 9.2 percent conjunctivitis?**

A. **That is approximately six percent difference. When**

you figure that there are probably half a million Americans on this medication, half a million people in the U.S., the six-percent decrease would be 30,000 less patients with allergic conjunctivitis. That means less people who can't take the medication, less phone calls to physicians, less unhappy patients. This is felt to be a very meaningful difference.

Q. Are there additional a results that are not recorded in the table that you reviewed?

A. Yes, again I was concerned about somnolence and asthenia. Although not a focus of this paper, those were also significantly less with the Alphagan P than with Alphagan.

Q. Were you surprised at the results?

MR. BREISBLATT: Objection. Again, he is not listed as an expert witness.

MR. SINGER: May I ask was he surprised at the time just as a factual question?

THE COURT: I will permit that.

BY MR. SINGER:

Q. Were you surprised at the time by the results?

A. I was very surprised by the results. When I first came to Allergan and I learned about the project, I was not sure that the formulation would increase the bioavailability to get more in the eye to get the exact pressure lowering

compatibility that the FDA requires and to be able to demonstrate the striking side effect benefit.

Q. **Thank you, Your Honor.**

Dr. Whitcup, did there come a time when the FDA approved Alphagan P?

A. **Yes. It was approved in, I believe it was the fall of 2001.**

Q. **Did there come a time when Allergan withdrew the Alphagan product?**

A. **Yes, they did.**

Q. **Did you support that withdrawal at the time?**

A. **I did.**

Q. **And why was that?**

A. **We had data to show that Alphagan P had exactly comparable pressure lowering, which is what the patients wanted to see from an efficacy standpoint. And looking at the totality of the data there was a clear safety benefit.**

Q. **Did you have discussions with the FDA about that withdrawal before it occurred?**

A. **Yes. Actually, on initial approval they had asked whether there were plans to potentially withdraw.**

Q. **What did you tell them?**

A. **We were considering withdrawing it.**

Q. **Once it was withdrawn, were there proceedings at the FDA over the withdrawal?**

A. **Allergan did file a citizens' petition, as was discussed by Ms. Brooks this morning, discussing the withdrawal of the base Alphagan product.**

Q. **And you have in your -- you should have in your book what is marked as DTX-335. Do you have that there?**

A. **Yes.**

Q. **Is that the FDA's response to the citizens' petition?**

A. **Yes.**

Q. **Can we have that up on the screen.**

I am going to read the conclusion that Ms. Brooks highlighted in her opening, which was on the last page: "Therefore, we disagree with your assertion," your being Allergan, "that Alphagan P .15 percent" -- if we could put the last page up to help the Court follow along -- "Therefore, we disagree with your assertion that Alphagan P 0.15 percent is safer and more effective than Alphagan .2 percent and reject your contention that Alphagan .2 percent was withdrawn for safety or effectiveness reasons."

Did I read that correctly?

A. **Yes.**

Q. **Did you agree with that at the time of citizens' petition decision?**

MR. BREISBLATT: Objection, relevancy as to whether he agrees with it or not. That is the FDA's decision.

THE COURT: Overruled.

THE WITNESS: No, I did not agree.

BY MR. SINGER:

Q. **Why not?**

A. **We had clear-cut data on allergy and somnolence and asthenia that showed that it was safer, that was borne out by the treating physicians as well who started using the product.**

MR. SINGER: Your Honor, I am at a convenient breaking point if you want to break. I can finish up in about six or seven minutes.

THE COURT: Let's do that.

MR. SINGER: Thank you.

BY MR. SINGER:

Q. **Dr. Whitcup, since Allergan brought Alphagan P .15 percent to the market, has Allergan done anything further to try to improve the product?**

A. **Yes. You know, though we had a substantial decrease in the side effects that we see with brimonidine, that didn't go to zero, we still got some patient complaints of somnolence and some of the other side effects. We talked to the formulators and said, could we decrease the concentration further, and could you, with the formulation, improve the bioavailability, so we got more in the eye so we could -- because we knew we needed to keep the same IOP**

lowering. The FDA wouldn't allow us to get a comparable product unless the IOP were the same. So the formulators said yes, and we did undertake a program to look at .1 percent brimonidine as well.

Q. **What was the result of that project?**

A. **The result was that again we showed comparable equivalent IOP lowering, met the FDA definition, the 95-percent confidence intervals being within the margins they set. When you look at the totality of safety data, again, it showed some safety benefit for patients.**

Q. **Is that the Alphagan P 1-percent product?**

A. **That is.**

Q. **That is on the market today as well?**

A. **That is.**

Q. **In your book, let me ask one more question, was there a clinical study, a report done for the FDA like the ones for Alphagan P .15 percent?**

A. **Yes, there is a 12-month complete study report that summarizes both efficacy and safety over a one-year period.**

Q. **Hopefully you have in your book Pages 188435 to 40 of JTX-102. Is that there, sir?**

A. **Yes.**

Q. **Can you identify this document for the Court, please?**

A. **Yes. That's the 12-month complete study report for the pivotal Phase 3 trial for the Alphagan P 0.1 percent**

product.

Q. **And is this part of the NDA for the Alphagan P .1 percent product?**

A. **Yes.**

Q. **Is there a methodology you can point to as we did in the Katz paper for the study?**

A. **If you go to the synopsis on Page 3, under Methodology, you can see that it describes the method of the Phase 3 trial.**

Q. **What was being studied there?**

A. **So here we were comparing the new formulation, the brimonidine Purite 0.1 percent to the base Alphagan. It was again a randomized trial, so patients were randomly assigned to one of those two treatments. And it talks about the visit schedule, again, the FDA had very strict times at which you measured all the intraocular pressures.**

Q. **Why wasn't it compared to the Alphagan P .15 percent?**

A. **Again, you know, the FDA -- one of their primary concerns is efficacy, and where possible they always make you measure back to the original product just in case there were 12 iterations of a product, each almost imperceptibly less effective than the first one, you could get a stepping effect. So they always have you compare back to the original, in the FDA's mind it is almost the best and fairest comparison. We are trying to say you are comparable**

or equivalent to the original Alphagan. So they made you say compare the original Alphagan.

Q. **Are the efficacy results reported in here?**

A. **Yes, they are.**

Q. **Where can we find those?**

THE COURT: Doctor, would you explain what stepping effect is?

THE WITNESS: Sure. The FDA had requirements to be comparable. If you were slightly less but not -- you know, not inferior enough that you triggered their definition of being not as effective, then you did another one, and you were again imperceptibly or slightly less effective than your drug 2, and you kept doing those, at the end of the day, you might be far away from the original Alphagan. So they make you compare to the original so that, even with the strict definition, there is no chance that you sort of are a little bit less effective each time. But after five or six of these, you add them all up, you are now three or four millimeters worse when each time you might have been .3 millimeters worse. They always have you go back to the original one.

MR. SINGER: Thank you, Your Honor.

BY MR. SINGER:

Q. **I asked before His Honor asked the question where the efficacy results are in the documents.**

A. **If you look, there is a summary of the pressure measurements on Page 5, if you look at the bottom half, this just gives you an be idea of the criteria that the FDA used. So you needed to measure this at multiple hours, at multiple visits.**

Again, one of the reasons I was surprised we could do this and even more surprised at the .1 percent was just the strict definition, and just the rigor of needing to measure the pressure so thoroughly and at so many time points.

Q. **And were the results also on adverse events that were significant as well?**

A. **Yes. If you go to the safety section, which can be seen on Page 7, it summarizes some of the main safety benefits. If you look at the first couple of paragraphs, I will focus on a couple of things. One, if you look at a the first sentence in the second paragraph, where it says Treatment related adverse events, so those were significantly different, again, at .014. We also noted that discontinuations were less.**

If you look at adverse events that forced the patient to stop, it's in the last paragraph, that was also significantly lower for patients using the Alphagan P .1 than the base Alphagan.

Again, I always looked at safety and looked back

to asthenia and oral dryness. If you go to the top paragraph, the last sentence, you can see that again a sentinel symptom of oral dryness was lower as was asthenia.

Again, we are seeing the same benefits that we had hoped for. Less side effects for the patient but equivalent IOP.

MR. SINGER: Thank you, Dr. Whitcup. I have no further questions at this time.

THE COURT: Thank you, Doctor. We will have cross-examination after lunch. Let's come back at 1:30.

(Luncheon recess taken.)

THE COURT: Counsel, please stay seated.

Counsel, a housekeeping matter for tomorrow. I have a rather important issue that I am dealing with. It's going to affect the schedule for tomorrow. You are going to need to be flexible. My present plan is to begin at the 9:00 hour and to work until 10:15, and then resume between 2 and 2:15, depending upon my late morning and early afternoon.

Okay. Cross.

THE COURT: And we will go until 6:00 tomorrow.

CROSS-EXAMINATION

BY MR. BREISBLATT:

Q. Do you still have your book there that you were handed with your exhibits?

A. **No, I don't.**

Q. **May I please have it?**

MR. BREISBLATT: Your Honor, does the Court still have its copy of the book?

THE COURT: I do.

BY MR. BREISBLATT:

Q. **Dr. Whitcup, I would like you to look at DTX-335. I believe you referred to it in your direct examination. That is the FDA letter. Do you recall that?**

A. **Yes.**

Q. **I would like to take you to Page AGN 0224688, and you were employed by Allergan at the time that this letter was written. Correct?**

A. **The response -- yes.**

Q. **Now, I would like to look at the first sentence, go down to the last paragraph on that Page 10, I am going to focus on the sentence that begins with, "When Allergan withdrew Alphagan 0.2 percent." Do you see that?**

A. **Yes.**

Q. **Now, the FDA suggested that you did not, Allergan did not cause itself significant harm because it waited until it was able to supply adequate amounts of Alphagan P 0.15 to cover Alphagan 0.2 prescriptions before implementing the withdrawal. Do you see that?**

A. **Yes, I do.**

Q. **In fact, that's what happened, isn't it?**

A. **I wasn't involved in that.**

Q. **That's not my question, sir. That's what happened. In other words, Allergan kept Alphagan .2 percent on the market until it had enough Alphagan .15 to cover the prescriptions. Isn't that correct, sir?**

A. **That's what it says.**

Q. **And, in fact, Allergan still sells Alphagan 2 percent in Europe, doesn't it?**

A. **Yes, it does. But the --**

Q. **Does it sell .2 percent in Europe, sir?**

A. **I answered yes.**

Q. **Thank you.**

MR. SINGER: If the witness could be permitted to finish his answer, I would appreciate it.

THE COURT: That is fair. I understand this is cross-examination, counsel. But let the witness finish his answer.

THE WITNESS: We don't sell it because the European requirements for preservatives are different, so we could not get the .15 percent approved.

BY MR. BREISBLATT:

Q. **You could have taken .2 percent off the market if you thought it was a safety and health problem, couldn't you?**

A. **We could.**

Q. **Now, the FDA's said, if anything, Allergan's decision economically benefited the company by removing from the market a drug that was subject to imminent generic competition on the Alphagan 2 percent. And that's what was about to happen. Right? Allergan knew that generic versions of .2 percent were going to be hitting the marketplace. Am I correct?**

A. **Correct.**

Q. **And shifting the vast majority of prescriptions for the remaining drug Alphagan .15, which was not facing imminent generic competition, and that's what you did. Am I correct?**

A. **There was a shift to what we thought was a safer product.**

Q. **But you took the .2 percent off and you shifted the doctors to .15 before the generic competition could begin. Correct?**

A. **It was before the generic competition, but after approval.**

Q. **And then Allergan is no doubt aware that even if an ANDA referring to Alphagan 0.2 percent is approved, it cannot be rated therapeutically equivalent, and, therefore, substitutable to Alphagan P 0.15, the product remaining on the market. Isn't that correct?**

A. **That's correct.**

Q. **And the FDA found that Allergan had gained economic advantage through the withdrawal of the Alphagan 2 percent. Isn't that correct?**

A. **It hypothesized that.**

Q. **Now, are you familiar as to the date when the NDA was filed for Alphagan P .15?**

A. **No, I don't recall the exact date.**

Q. **Would it refresh your recollection if I showed you the cover page and it showed a date of June 29, '00?**

A. **I am sure if that's the correct date --**

Q. **Let me show you a copy of GTX-101 A and let me ask if this refreshes your recollection?**

THE COURT: Counsel, you would like to approach the witness?

MR. BREISBLATT: I am sorry, Your Honor. May I approach the witness?

THE COURT: Yes, you may. And you have leave to approach freely.

BY MR. BREISBLATT:

Q. **If you look at the second page, does that refresh your recollection as to the filing date of the NDA for Alphagan P .15?**

A. **Yes, it appears to be 2/29/2000.**

Q. **Is it fair to say by June 29th, 2000, Alphagan believed that the .15 was the best mode for making a**

brimonidine tartrate glaucoma medication?

A. **We felt by then that if approved and available for patients, it was the safer medication, absolutely.**

Q. **Now, when you file an NDA and it is accepted, in this case, for the P .15, Alphagan received from the FDA three years of exclusivity, did it not?**

A. **I believe so, yes.**

Q. **And during that period of time, no generic could come on the marketplace even if you didn't have any patent protection. Isn't that correct?**

A. **Correct.**

Q. **Now, in the Allergan business model, that three years of exclusivity is not enough, is it?**

A. **I am not sure what the question is. Not enough for what?**

THE COURT: If you are not sure, just say you are not sure.

THE WITNESS: I am not sure.

BY MR. BREISBLATT:

Q. **That what Allergan really shoots for is to get patent protection for its products. Correct?**

A. **I think that's always one of the considerations. The key consideration, you know, as well as to have a better product for patients.**

Q. **But it is a key consideration, patent protection. Am**

I correct?

A. That is one consideration, yes.

Q. Because that will extend out the period of time of exclusivity. Am I correct?

A. If you have patent protection, that would do that, yes.

Q. Now, the Alphagan family of products, is that a major product for Allergan?

A. It's one of our major products.

Q. Very profitable line?

A. It is not the most profitable but it is an important medication that we sell.

Q. And a profitable one. Correct?

A. Yes.

Q. In the case of the Alphagan P, even though you were not there, you learned that the way that they came up with this product is combining the Alphagan Refresh Tears product with brimonidine tartrate. Correct?

A. My understanding, although I am not a formulator, is it wasn't as simple as taking two known products and combining them.

Q. That wasn't my question. They took the Refresh Tears formulation and combined it with brimonidine tartrate. Isn't that correct?

A. Again, I am not a formulation expert, so I don't know

what was exactly in the Refresh Tears formulation and if it's really an exact combination.

Q. And the Refresh Tears product was a patented product, wasn't it?

A. I believe that the Purite preservative was patent protected.

Q. Let me show you what has been marked as DTX-021. Do you recognize this as being Brimo X being the formulation for Alphagan P?

A. Again --

Q. I know you are not a formulator, but do you recognize that as being the ingredients within it?

A. Parts of it, yes. Parts of it, to be honest, no.

Q. If you look over to the Refresh Tears, you see where it contains, other than the brimonidine tartrate, the same ingredients. Do you see that?

A. Yes, I see it.

MR. BREISBLATT: If I may have a moment, Your Honor?

THE COURT: Yes.

(Pause.)

BY MR. BREISBLATT:

Q. Now, you would agree with me, would you not, at least in 1999, which is before the Katz study -- the Katz study you have in front of you. Do you still have that in your

book? I believe it is --

A. I have it.

Q. EDTX-099?

What is the date of that?

A. I am looking myself.

Q. I believe if you look down at the bottom on that first page, you see where it says, Received May 9, 2001; Accepted August 7, 2001?

A. Right. So it was published sometime after that.

Q. Sometime after 2001?

A. Well, sometime after August.

Q. August 2001. And you would agree with me, though, in the summer of 1999, there really hadn't been any authoritative studies done on whether there was allergies caused by brimonidine tartrate. Correct? Or you have not seen one, at least?

A. I wasn't at Allergan then, but I am fairly sure that there was a number of reports of severe allergy with brimonidine prior to that.

Q. Allergies, but no substantial report like the Katz report comparing .15 to .20. Am I correct?

A. That is correct.

Q. And it was known that BAK caused irritation, you have testified about that. Correct?

A. Not nearly in the same vein. The irritation you get

with BAK is really not like what was shown today.

Q. **Let me show you what has been marked as DTX-10.**

THE COURT: I have given you free leave to approach this witness. Just with each witness, ask for liberty to approach that witness.

MR. BREISBLATT: Thank you.

BY MR. BREISBLATT:

Q. **Do you have DTX-10 in front of you?**

A. **Yes.**

Q. **It is a pretty thick document, so I will direct you to AGN 00059381. And you know what numbers I am talking about? The little Bates numbers at the bottom?**

A. **Yes.**

Q. **And you understood this to be an Allergan internal document dated January 24, 2000. Am I correct?**

A. **Yes.**

Q. **If you look at AGN 59381, do you see at least in January 24, 2000 at Allergan, the replacement of BAK with Purite was initiated in an effort to improve the efficacy and/or tolerability of Alphagan formulation. Do you see that?**

A. **Yes.**

Q. **"Although BAK has been safely used in numerous ophthalmic preparations, it is known to induce corneal epithelial toxicity and cause allergic reactions in some**

patients." And it cites to some literature. Is that correct?

A. **That's correct.**

Q. **The literature it cites to all predates July of 1999. Am I correct?**

A. **That's correct.**

Q. **Finally, Doctor, a general proposition. If one wants to eliminate or limit side effects, one of the things they can do is limit the dose of the active ingredient. Am I correct?**

A. **To limit side effects, you can -- the issue is can you maintain efficacy at the same time?**

Q. **One way to deal with side effects is to lower the drug dose. Am I correct?**

A. **That's correct.**

MR. BREISBLATT: No further questions.

THE COURT: Any redirect?

I am sorry. I apologize. Mr. Boggs.

MR. BOGGS: That's okay.

BY MR. BOGGS:

Q. **Hello, Mr. Whitcup.**

When you first started your direct testimony, you were describing Phase 1, Phase 2, and Phase 3 clinical trials. What is done in a Phase 1 trial?

A. **Phase 1 trials assess predominantly safety of the**

medication.

Q. **Safety issues. Is that right?**

A. **Correct.**

Q. **What's done in Phase 2 trials?**

A. **Phase 2 expands upon the safety and looks at efficacy of the medication.**

Q. **Now, you mentioned before Alphagan P .15 percent brimonidine. Was that the first product you worked with at Allergan?**

A. **One of the first ones when I came to the company was that .15 percent.**

Q. **What were the results of the Phase 2 trials for Alphagan .15 percent P?**

A. **Both studies were done prior to my arriving at Allergan. But I have seen publications of the results that showed that there was a dose response to brimonidine for lowering intraocular pressure.**

Q. **For a .15 percent formulation?**

A. **I believe the study looked at .08, that was shown this morning as well, .2, .5.**

Q. **There were no Phase 2 trials done with .15 percent brimonidine. Isn't that correct?**

A. **That's correct. .15 was based on pharmacokinetic data that we had with the new formulation.**

Q. **So no safety Phase 1 trials were done and no safety**

and efficacy Phase 2 trials were done. Is that right?

A. **Well, it is not exactly true. We did pharmacokinetic studies. But what the FDA wanted to see was what was the patient actually exposed to. What we showed them, both in patients and in our animal models, was that by changing the formulation, we could lower to .15, get the same amount in the eye, but have less in the blood. That allowed the FDA to accept our .15 percent.**

Q. **Mr. Whitcup, Allergan went straight to Phase 3 trials with the .15 P formulation. Isn't that right?**

A. **No, that's not correct. Again, we did pharmacokinetic studies. Initially, we did dose ranging in Phase 2 and then presented data to the FDA after those studies to justify the doses we picked for Phase 3. That is always an important part before you go into Phase 3 is to have conversations with the agency. And those were all done.**

Q. **Were there Phase 2 trials done with .15 P?**

A. **Yes. Again, not with that specific dose. But trials that justified the use of that dose.**

Q. **So you predicted the .15 would do just fine in Phase 3 . Is that right?**

A. **Well, actually, we didn't. We picked that as one of the dosages, but we also put a .2 in there, because, given guidance from the FDA, they said we have a very strict hurdle rate to be comparable, and there were people at**

Allergan who didn't think that the change in formulation would improve the bioavailability enough at that point, .15, that it would meet the FDA hurdle and that's why we actually put two doses in Phase 3. If we were sure .15 would work, we would have never put the .2 in.

Q. **What is involved in a Phase 3 trial?**

A. **Phase 3 trials, the FDA gives you pretty standard ways to measure pressure. At least for glaucoma, you know exactly what you want to do. They tell you when and how to measure the pressure, you put the patients with glaucoma into the study, dose them, and measures the pressures as the FDA says.**

Q. **They are very costly, aren't they?**

A. **You know, again, the nice thing about glaucoma studies is you know how to do them. So in the scheme of the products we develop, you know, they are not inexpensive, but they are among the less expensive trials that we do, just because they are standard approaches to those patients.**

Q. **You have talked about those boxes over there earlier. Is that one NDA or two NDAs?**

A. **I believe that's just the Alphagan P NDA. So single NDA.**

Q. **Alphagan P .15?**

A. **Correct.**

Q. **There is nine boxes?**

A. **Correct.**
Q. **And you say that's a standard size for an NDA?**
A. **Correct.**
Q. **Now, are there, in an NDA, manufacturing instructions?**
A. **I believe there is a manufacturing section that is included, yes.**
Q. **And that manufacturing section explains how the product is made. Is that right?**
A. **Part of those sections talk about manufacturing.**
Q. **And what happens if you deviate from those manufacturing instructions?**
A. **I am not, you know, I am not the manufacturing expert. But there are FDA guidelines that you -- that get reviewed. And if you fail to meet certain FDA regulations, then the New Drug Application won't be approved.**
Q. **What if it's approved and you deviate from those manufacturing instructions, can you sell that product?**
A. **If the FDA becomes aware, there are certain -- it depends what the deviation is. Some you can explain to the agency, and as long as they are corrective measures, or you explain why there is no impact to the patients, you may be able to change the specification. If it's a deviation that puts patients at risk, clearly, you shouldn't and we wouldn't sell that medication.**
Q. **I would like to look at the picture of allergic**

conjunctivitis, ADX-7?

Dr. Whitcup, is this your patient?

A. **This is not my patient.**

Q. **Where did this picture come from?**

A. **I am not exactly sure where this photograph came from. I believe it was from an academy publication. But I am not sure.**

Q. **There is something wrong with that patient's nose. Do you know what's wrong with that?**

A. **I am not sure.**

Q. **So you can't even testify with certainty that this person was taking Alphagan. Is that right?**

A. **Since I didn't see this specific patient, I can't testify. I can tell you that I have seen many patients with allergic conjunctivitis from Alphagan that look very much the same as this patient.**

Q. **Did you bring any pictures of them with you?**

A. **No, I did not.**

MR. BOGGS: No further questions. Thank you.

THE COURT: Redirect, Mr. Singer.

MR. SINGER: May I have redirect for two minutes.

THE COURT: Yes. That's what I was offering. If you want to take longer than two minutes, you may.

REDIRECT EXAMINATION

^ **BY MR. SINGER:**

Q. **I just wanted to give you a chance, Dr. Whitcup, to follow up on something that counsel asked. If I can refer you, I believe it was DTX-10, the portion about the BAK, it was on that big thick document, AGN 0059381.**

Do you have that in front of you?

A. **Yes.**

Q. **Counsel referred to the sentence that although BAK has been safely used in numerous ophthalmic preparations, it is known to cause corneal epithelial toxicity and cause allergic reactions in certain patients. And I believe you commented that it was very different than the patient Mr. Boggs put up. What did you mean, "it was different"?**

A. **Two points. One, the epithelial toxicity in some patients causes mild discomfort. There are rare cases of allergy, but in the range of maybe one percent or less. We have BAK in many, many of our products and don't see anything at all that looks like the rate and the type of allergy we have seen with Alphagan.**

So although BAK is known to cause some ocular side effects, they tend to be much more mild than we saw with Alphagan and the allergy much rarer. In fact, as I said before, the leading glaucoma product, Zalton, has a lot of BAK. You just don't see any similar side effects in scope or in frequency to what we saw with Alphagan.

When I looked at it, if you can have a better preservative, that is a plus, but I didn't think changing the BAK would at all address the allergy problem that we had with Alphagan.

Q. **What did you attribute the allergy improvement to in the Alphagan P product?**

A. **Less drug.**

MR. SINGER: Thank you, I have nothing further.

THE COURT: Thank you, Doctor.

THE WITNESS: Thank you.

(Witness excused.)

MR. SINGER: Your Honor, we don't plan to recall Dr. Whitcup. May he stay in the courtroom.

MR. BREISBLATT: We have no objection, Your Honor.

MR. BOGGS: No objection.

MR. SINGER: Thank you, counsel.

THE COURT: Certainly.

MR. SINGER: Thank you, Your Honor.

MS. BROOKS: Your Honor, Allergan would call as its next witness Dr. Olejnik.

OREST OLEJNIK, having been duly sworn as a witness, was examined and testified as follows:

MS. BROOKS: Your Honor, might I approach the witness to give him an exhibit binder?

THE COURT: You have leave to approach the witness, Ms. Brooks.

MS. BROOKS: Thank you, Your Honor.

Your Honor, before I forget, Dr. Olejnik has a medical condition that might require him to take very sudden breaks. Hopefully not. But with the Court's permission, if he does, we may just ask the Court for a break and be excused.

THE COURT: Just let me know, Doctor. We will both take a break.

MS. BROOKS: Thank you, Your Honor.

DIRECT EXAMINATION

^ BY MS. BROOKS:

Q. **Good afternoon, Dr. Olejnik.**

A. **Good afternoon.**

Q. **I can hardly see you with that monitor there.**

A. **Good afternoon. Does this chair --**

THE COURT: It doesn't move. It's the government's way of maintaining control? I don't know.

MS. BROOKS: It is a bad combination of a big monitor and a short lawyer.

With the Court's permission, may I conduct the examination from here.

THE COURT: Absolutely.

MS. BROOKS: Thank you.

BY MS. BROOKS:

Q. **Dr. Olejnik, have you ever testified in a courtroom before?**

A. **No, I have not.**

Q. **Is it a bit intimidating?**

A. **I am trying to think. It will be a new experience, put it this way.**

Q. **Well, if at any point I or opposing counsel ask a question you don't understand or if we go too fast, will you please just let us know?**

A. **I will.**

Q. **Thank you. Can you tell the Court, please, where you work?**

A. **I work at Allergan, in Irvine, California.**

Q. **How long have you worked there?**

A. **Over 17 years. It will be almost 18 years in July.**

Q. **What is your current position at Allergan?**

A. **I am a senior vice president of global pharmaceutical sciences.**

Q. **What does that mean?**

A. **It means, it covers many discipline functions within that pharmaceutical sciences area. And, essentially, it's the pre-formulation, understanding the physical and chemical characteristics of API, the drug substance, the active pharmaceutical ingredient, developing the formulations to be**

safe, effective, fit for use for the patient.

It involves manufacturing of formulations, understanding how to scale them up for manufacturer, large scale, it includes manufacturer for clinical supplies, for safety studies, flexibility studies, we do get involved in a lot of the method analytical developments to understand again the key aspects of the formulation. Finally, providing all of the data that we generate in that field, the chemical, manufacturing, and control section that goes into a dossier to the agency, whether it be the FDA or other agencies worldwide.

Q. **That sounds like a lot of stuff that you oversee?**

A. **It does. I have good people that do that as well.**

Q. **How many people do you have that report to you either directly or indirectly in your position?**

A. **Approximately 300 people.**

Q. **Now, I would like to back up a little bit then and talk a little about your background that would enable you to have the sort of position that you have at Allergan.**

Do you have a Ph.D.?

A. **Yes, I do.**

Q. **Could you tell the Court what your Ph.D. is in?**

A. **It is a Ph.D. in ion association, species and drug transport. It is in pharmaceutics, essentially.**

Q. **Did you just say that you got your Ph.D. in ion**

association, and could you repeat the rest of it, please?

A. **Species and drug transport.**

Q. **Ion association species and drug transport. That was the title of your thesis?**

A. **I think it was the title. Whether "species" is in there, I don't know. But it was ion association drug transport.**

Q. **What year did you get your Ph.D.?**

A. **That was in 1981. Convocation was in December of 1981.**

Q. **Convocation?**

A. **Yes.**

Q. **Can you explain, I think that may be a British term, so can you explain to us what convocation is as far as a Ph.D.?**

A. **After going through your viability, defending the thesis, which it feels like I am doing here now, there is a natural official ceremony where the Ph.D. is bestowed on the student. And that occurred, I think it was on the 12th of December.**

Q. **What university was that?**

A. **That was the University of Nottingham.**

Q. **So I detect a British accent?**

A. **It is a British accent. The name may not suggest it. But I was born and raised in the U.K., yes.**

Q. **When did you come to the United States?**

A. **That was in April of 1984.**

Q. **After coming to the United States, did you work in the area of drug formulations at all?**

A. **Yes, I did.**

Q. **Could you tell the Court a little bit about that background?**

A. **Here in the U.S.?**

Q. **Sure. Or even starting in Great Britain, if it is pertinent.**

A. **I started with Sterling Winthrop prior to -- my first degree, undergraduate degree is in pharmacy. And after finishing the pharmacy degree, I went to work for Sterling Winthrop. As part of that was to also register with the Pharmaceutical Society of Great Britain, which required you to get experience with an industry, within the hospital, within the retail pharmacy side. The majority of my work was done at Sterling Winthrop. And I was involved in solid dosage forms, gels for dermatological products, suppositories. The full gamut of dosage forms.**

Q. **And after that, what happened?**

A. **After that, I went to Nottingham University to do my Ph.D. After I finished that, I went to Fisons Pharmaceuticals, which is now part of AstraZeneca. And I was focused in the pre-formulation area, providing all the**

physical-chemical characterization of compounds, excipients, that were, again, for a wide range of products, and some of the work with ophthalmic wholesalers, solid dosage forms, and so on.

Q. **Let me stop you there because you put a lot in that answer, some terms we may not be familiar with, including me. You said it's in the pre-formulation area. What is pre-formulation?**

A. **Pre-formulation is one where you are studying the aspects of the drug compound. You need to understand how it would behave one as its own substance. You need to know, is it stable enough just as a drug in a container. The pharmaceutical companies, they have their compounds, drug substances, synthesized.**

You need to fully understand, is that drug stable under conditions of light, in air, what other, heat, will heat cause the drug to degrade. You need to fully understand, again, the stability aspects of that compound. And then begin to understand its physical chemical behavior, the pKa, the solubility aspects of the drug.

If you are developing it as a solid dosage form, you want to understand its crystal behavior, does it change form? Does it become a polymorphic form, which, in of itself, could, in fact, be in a form that is completely insoluble in an aqueous system, indeed, when taken into the

body?

So there are many facets with regards to understanding just the preliminary aspects. Then again the behavior of excipients. You need to understand the behavior of the excipients in relation to the drug itself.

Q. **You mentioned the word "drug," and separate from that, you used the term "excipient." Are they different things?**

A. **Yes, they are.**

Q. **What is the difference between what you would refer to as a drug and what you would refer to as an excipient?**

A. **An excipient is an inactive ingredient that is brought together as a formulation with the drug, which is the active ingredient, to create a system that is amenable for administration to the patient, ultimately.**

Q. **And I heard you mention in your earlier answer something about having to know about the pKa of the drug. What is pKa?**

A. **The pKa basically defines what pH, in a very simplistic term, what pH will the drug be -- in a 50 percent - 50 percent ionized/non-ionized state.**

Q. **Now, moving ahead, you did all this pre-formulation work. What is the next company you worked for after that?**

A. **I then left Fisons to work for, I was going to go to Merck but I decided to go to this smaller company, it was out in Mountain, UCA, I didn't know what "CA" meant at the**

time, it ended up being California. I ended up working for a small company up in Northern California called Cooper Vision.

Q. **I take it Cooper Vision, based on the last part of that title, dealt with ophthalmic?**

A. **It was ophthalmic. A lot of contact lens care, as well as ophthalmic drug products.**

Q. **What time period are we talking about now?**

A. **That was in April of 1984. I remember it well. When I arrived, there was an earthquake in Morgan Hill, which was quite an interesting experience.**

Q. **I take it you had not been in an earthquake before?**

A. **No, I had not.**

Q. **My apologies from the State of California?**

A. **And the wrath of my mother at times.**

Q. **But you are still in California now?**

A. **Yes, I am.**

Q. **So based on what you have told us, so we can kind of fast-forward to your really extensive work history, at some point, did you work for Johnson & Johnson?**

A. **Yes, I did. At one point in time, Cooper Vision, the pharmaceutical side of the business which I was a part of, Johnson & Johnson acquired that business.**

Q. **So would it be fair to say that you have worked in the area of pre-formulations and formulations of ophthalmic for**

over three decades?
A. Yes. Sounds rather long. But, yes.
Q. That is the first time you counted it up.
So, Dr. Olejnik, during the course of all of that time, did you obtain, were you listed as an inventor on any United States patents?
A. Yes, I was.
Q. And, specifically, if you could turn in your binder to what has been marked as JTX-002, JTX-003, JTX-004, and JTX-005, and please tell the Court -- they are already in evidence -- what these four patents are?
A. Well, JTX-003 is the composition containing therapeutically active components having enhanced solubility.
Q. You are going to have to slow down, I am afraid, so the court reporter can get that down.
Could you say again what that is?
A. Compositions containing therapeutically active components having enhanced solubility.
Q. And what number was that?
A. That was JTX-002, I might have said 003. It's JTX-002.
Q. Is that the '873 patent?
A. That is the '873 patent, correct.
Q. Are you a listed inventor along with Dr. Kerslake?

A. **Yes, I am.**

Q. **And now, JTX-003, is that the '210 patent?**

A. **JTX-003 is the '210 patent.**

Q. **Are you also a listed inventor on that patent?**

A. **Yes, I am.**

Q. **JTX-004, is that the '834 patent?**

A. **JTX-004, that is the '834 patent.**

Q. **And, again, are you a listed inventor along with Dr. Kerslake on that patent?**

A. **Yes, I am.**

Q. **JTX-005, is that the '337 patent?**

A. **JTX-005, that is the '337 patent.**

Q. **Are you a listed inventor on that patent along with Dr. Kerslake?**

A. **Yes, I am.**

Q. **We are going to come back in a little bit to talk about the patents themselves. But what I would like to do now is back up to how you came to create the inventions that are the subject of the four patents that we just talked about.**

Okay?

A. **Yes.**

Q. **So when you came to Allergan in 1991, was anyone at Allergan working on a formulation involving brimonidine?**

A. **Yes, they were.**

Q. **And what were they working on?**

A. **They were working on what became the Alphagan .2 percent product.**

Q. **Now, we have heard about the Alphagan .2 percent product. When you refer to .2 percent, does that mean the brimonidine is at a .2 percent amount?**

A. **That was the brimonidine tartrate .2 percent.**

Q. **If you could look, please, in your binder, at JTX-101, it is a joint exhibit, and, specifically, if we could have Bates No. 8769 put up. If we could have blown up, it is really not very good print, but it's the best copy we have, the very first sentence says, Alphagan, under Description, so we have Alphagan brimonidine tartrate ophthalmic solution .2 percent.**

Is that the formulation that they were working on at Allergan when you arrived in 1991?

A. **That is correct, yes.**

Q. **And then if we could go down below the molecular structure, there is a sentence that says, The pH of 6.3 to 6.5. It is right above where it says, Clinical pharmacology. There we go. Do you see that?**

A. **Yes, I do.**

Q. **Now, did you work on this actual formulation? If we could leave that up there, thank you. Did you work on this actual formulation?**

A. **No. Only indirectly in terms of filing the proving reports and involved in filing the NDA.**

Q. **You saw, obviously, at some point, what this formulation was going to be, the amount of brimonidine and what the pH was going to be?**

A. **Yes, I did.**

Q. **And when you saw that the pH of Alphagan was going to be approximately 6.3 to 6.5, did you have any questions regarding that?**

A. **Well, I had concerns that it was in an acidic region from all the work that I have done in the past and knowledge about the complexities of the eye and so on. It's preferable, as part of a formulation focus, to achieve physiological pH.**

This was not physiological pH. This was in the acidic region.

Q. **In fact, could we put up ADX-5, please. Just so we know what we are talking about and can orient ourselves, when you say "acidic region," we have put up here a big "I" and it says pH 7.4. Is that the pH of the eye?**

A. **It is the pH of the eye.**

Q. **When I say the eye, is it actually the tears of the eye?**

A. **It's the tears. Generally, it is higher than 7. There are varieties of pHs. But, for the most part, people**

recognize 7.4 as the pH of the tear.

Q. **And on this pH scale, where is neutral?**

A. **Neutral is 7.**

Q. **So if you are lower than 7 with your pH, is that considered an acidic pH?**

A. **You are in the acidic region, yes. You are beginning to go into the acid side, yes.**

Q. **If you are higher than 7, is that then considered an alkaline or base pH?**

A. **It is more alkaline, more base, yes.**

Q. **So if I heard you correctly, you had questions why Alphagan P was -- excuse me -- Alphagan was being formulated down here, all the way down at approximately 6.3 to 6.5. Is that right?**

A. **That is correct.**

Q. **So what if anything did you do with those questions?**

A. **Well, the principal formulator at the time, Dr. Shulin Ding, I actually questioned as to why would you be developing a product under acidic conditions. And particularly when this product is going to be used chronically in the treatment of glaucoma.**

Q. **When you say "chronically," what do you mean?**

A. **It means it's going to be repeatedly used each and every day throughout the life of the patient, assuming that they have glaucoma, for that period of time.**

Q. **Did you receive a response to your questions?**

A. **Yes, I did.**

Q. **What was the response?**

MR. BREISBLATT: Objection. Hearsay.

MS. BROOKS: Your Honor, we are not offering it for the truth of the matter asserted but for Dr. Olejnik's state of mind and why he did what he did. In fact, the response turned out not to be accurate.

THE COURT: Do you want to withdraw the objection, with that explanation?

MR. BREISBLATT: No. I think I will copy it. It's still hearsay.

THE COURT: I will overrule it.

BY MS. BROOKS:

Q. **Dr. Olejnik, did you receive a response to your questions?**

A. **Yes, I did.**

Q. **Could you please tell the Court what that response was?**

A. **It couldn't be formulated in physiological pH because the brimonidine would precipitate out. It wasn't soluble enough to achieve that pH.**

Q. **That's what Dr. Shulin Ding told you?**

A. **That is correct.**

Q. **And what if anything did you do with that information?**

A. **Well, based on the solubility profile she had and recognizing the work that she had been involved in, I fully understand that that was an issue. And I left it at that.**

Q. **Now, you say that it's based on the work that she had done and the solubility profile. Did any of the solubility work that had already been done at that point make its way into the patents that we have just discussed?**

A. **Yes, they did.**

Q. **Could you specifically go back to the '210 patent, which is JTX-003, and could we put Table 2 up there, please?**

It's on the screen, also, Dr. Olejnik, if it saves you time. What are we looking at here when we look at Table 2, which is in the '210 patent at Column 14, starting at Line 25?

A. **It's a solubility study that was conducted by one of the professionals in Shulin's group. It's looking at the effect of pH on solubility.**

Q. **The effect of pH on the solubility of what?**

A. **Of brimonidine tartrate.**

Q. **Had you seen this data before?**

A. **Yes, I had.**

Q. **Was it done -- were these studies done in approximately 1994?**

A. **I would need to go back and check the actual report as to which date. But it would have been around that time**

period, yes.

Q. **What does this data show us?**

A. **Well, the data is showing you that as the pH increases, the solubility of brimonidine tartrate decreases.**

Q. **Now, when this table, by the way, was taken out from the lab notebook and made its way into the patent, was there a mistake made on this particular chart?**

A. **Yes, there was.**

Q. **Where is the mistake?**

A. **I think that's at the bottom of, I think it's line 49, where it says, I think that's an "E," is it not? I can't read it from here. It says, "percent weight per volume." That is incorrect. It should read, milligrams per ml.**

Q. **If we could blow up where it says "percent weight per volume." Right there. The very last one. Right there. There we go.**

So you are saying instead of saying percent weight per volume, it should say what?

A. **Milligrams per ml.**

Q. **Does that mistake change at all, though, what this table is showing as far as the solubility of brimonidine vis-a-vis pH?**

A. **No. It still holds true that as pH increases, solubility decreases.**

Q. **Let's fast-forward if we could. Did there come a time**

when you and a group of others at Allergan were tasked with improving upon, if possible, the Alphagan formulation, the .2 percent brimonidine at a pH of 6.3 to 6.5?

A. **Yes, we were.**

Q. **And, specifically, did that project have a name?**

A. **It had a name, brimonidine X. We shortened it to Brimo X.**

Q. **Why was it called Brimo X? Why the X?**

A. **Because we didn't know what formulation we were going to develop at that point in time. We were aware of the challenges. But we needed to do a significant amount of formulation work to understand again what the final formulation would be.**

Q. **Well, Dr. Olejnik, we have heard from Apotex counsel that all you did was take brimonidine and stick it in a product called Refresh Tears and you had a new formulation?**

MR. BREISBLATT: Objection to the form of the question.

THE COURT: Please repeat the question.

BY MS. BROOKS:

Q. **Dr. Olejnik, we have heard that all that you actually did was take brimonidine and put it in Refresh Tears in order to create a new formulation. Is that what happened?**

THE COURT: Do you still object?

MR. BREISBLATT: Different question. I will

withdraw it.

BY MS. BROOKS:

Q. **Is that what happened?**

A. **No. I wish life were that simple, but it's not.**

Q. **Let's see what actually happened. If you could turn in your binder, please, to JTX- -- I am sorry, it is PTX-289. What are we looking at here, Dr. Olejnik?**

A. **It's showing a matrix of a variety of systems that were evaluated.**

Q. **And if we could go to the bottom right-hand corner next to PTX-289, can you tell me the date of this document?**

A. **That was December 1996.**

Q. **Thank you. Now if we could go back and blow up the left-hand column, what are we looking at -- first of all, it says "delivery system" at the top of that column. Do you see that?**

A. **Yes, I do.**

Q. **What is meant by "delivery system"?**

A. **It's developing a system that would deliver the compound in an appropriate manner to have a therapeutic effect.**

Q. **When you refer to the compound, are we talking in this case about brimonidine?**

A. **Yes, we are.**

Q. **What are you looking at here, when it has listed**

Carbopol, Norm Ophth Bottle, Bottle in Bottle, Ointment Tube, Emulsion, Standard Gel, can you take us through, please, in under an hour, if you can, a brief kind of snapshot what each of these formulations or potential formulations are?

A. **Certainly. So the first section on the Carbopol 1382 cellulosic synergel, we are looking at a variety of gels that we knew with these types of excipients, they had certain behaviors, and evaluating them. It's known that, again, as part of the, in the ocular field, you are having to deal with significant effects of mother nature, the eye is well designed because of the blinking reflex, the tearing, the elimination is such at a fast rate that we are looking at systems at that point in time to see whether we could retain the drug on the eye for a longer period of time.**

With it, also, is also you are developing a system that is highly viscous, it is a gel, and looking at how can we present this to the patient to ensure good, effective compliance and precise delivery of the product to the eye in a repeated, reproducible manner.

So we were also evaluating various container closure systems. That also involved looking at different tip sizes. One of the things with conventional dropper bottles is that the tip of the container closure system, it

will deliver on the order of 35 microliters. The human eye tolerates around seven, eight microliters, maybe up to 10 microliters.

So you are putting in an excessive amount that can overspill down to the lid margins. Indeed, that has been seen with various products in the past.

So we were looking, can we design a system that would also allow us to reduce the drop volume to a volume that was more compatible with the eye. Why would we do that? Because when you put in a very large amount of volume, it can stimulate the eye to start tearing.

That's not something you want to have happen because it's going to accelerate the drainage of the product away from the cornea, the eye itself, down the nasal lacrimal duct, and obviously eliminate it, and you could have a propensity, where there is a drug in there, to potentiate side effects because of systemic effects.

Q. **You just gave us a whole bunch of information there. Let's see if we can break it down a little bit.**

Let's go back to the fact that you are trying out gels.

First of all, in this time period, did Allergan already make artificial tear products?

A. **Yes. They were well-known for artificial tear products, yes, Liquid Film.**

Q. **You mentioned Liquid Film. In fact, Alphagan, the original Alphagan, was that actually in an artificial tear product?**

A. **It was in an artificial tear base, liquid film base, yes.**

Q. **But it was at a low pH?**

A. **A low pH, correct.**

Q. **Aren't most artificial tears, I believe, in fact, we heard from opposing counsel that artificial tear products are made to be at a neutral or alkaline pH because of the pH of the eye?**

MR. BREISBLATT: Objection to the form of the question.

THE COURT: Rephrase it.

BY MS. BROOKS:

Q. **Dr. Olejnik, is it your experience, with decades of ophthalmic, that normally artificial tear products are formulated so that they are close to the pH of the eye?**

A. **That's correct.**

Q. **So if the brimonidine in the original Alphagan product was in this liquid film tears, which is an artificial tear product, how did the formulators lower the pH in order to get it to be in the acid range?**

A. **Well, they would have to use hydrochloric acid to reduce the pH, which was, again, necessary to ensure that**

the drug remained in solution.

Q. **So this is in late '96. You know that Allergan has an artificial tear product. Why didn't you just take the brimonidine and stick it in an artificial tear product and be done with it?**

A. **Because we knew that brimonidine would be precipitated because of the solubility issues. There is nothing unique about an artificial tear in terms of knowing what the excipients were and the behavior of the excipients at that time. You wouldn't be gaining anything. You basically are developing another Alphagan .2 percent product or whatever concentration you would have. But you would still have to formulate it under acidic conditions to main a solution state, a liquid state.**

Q. **So you would have just ended up exactly back where you started?**

A. **Essentially, yes.**

Q. **So, instead, you are experimenting with gels, 11 different kinds here, or at least 11 different delivery systems. You mentioned that you wanted to use gels to see whether it would cause the brimonidine to stay on the eye longer. Why did you want to try to do that?**

A. **Well, we wanted to improve the bioavailability of the drug. We were also looking at tests, Can we reduce the drug concentration? If we do that, it's not going to be**

effective. Now you are getting below the potential for it to have a therapeutic effect, meaning certain clinical end points that would be expected of you when you would do the clinical studies.

So you needed to evaluate systems that would actually help you design a formulation to achieve certain criteria of performance for the product.

Q. **Let's move ahead, then, to JTX-098. This is a joint exhibit. Specifically, if we could go to Page 3, and under "Manufacture of Formulations," blow that up, please.**

Before we were looking at these 11 different gel formulations that you were experimenting with in late '96. Now we have moved to the February-March time period of 1997. Did I get that right?

A. **Correct.**

Q. **And are we now looking at yet more formulations in addition to the 11 that we just looked at?**

A. **Yes, we are. These are in addition to those that we had assessed.**

Q. **What are we looking at here, what formulations are these?**

A. **Well, we are looking and comparing it to the Alphagan, the "BT" represents the brimonidine tartrate. There is a carbopol and the hydroxy propyl methylcellulose at a .2 percent, .15, the concentrations are listed there. High**

velocities. Another carbopol, HPMC formulation. We investigated an Aquasite gel system, which was a company called Insite Vision. They were based up in Northern California. Looking at outside technologies.

Q. Let me stop you before we move onto the bottom two, which are suspensions. The three formulations that come before the bottom two, which are suspensions, they are all at a pH of 6.4.

Why are you still trying to formulate at this acidic pH?

A. Well, as much as we try, we still wanted to make sure that the drug, the brimonidine tartrate, remained in solution. It was important -- for drugs to have an effect, they have to be in solution first and foremost.

We were not able to actually develop a formulation, a composition, that would achieve physiological pH. We were still having many challenges in that area. So we were evaluating these systems under acidic conditions.

Q. I don't see, unless I am missing it here, anything about Refresh Tears yet?

A. No.

Q. Is that right?

A. That's correct.

Q. What's perfluorodecalin?

A. Perfluorodecalin is a unique liquid. It looks like

water, but it's twice the density. In other words, it is twice as heavy as water. But it has some very unique properties. And one of them is, because of its specific gravity, when squeezed out of a dropper bottle, you get little minute drops of around seven to eight microliters, which was ideal from, if you recall what I mentioned earlier, it was ideal in terms of dropping it into the eye and not stimulating a tearing effect.

It also had a lot of other properties with regards to the fact that it would not support microbial growth, and, therefore, one would not need a preservative in there.

There were benefits in terms of stabilization of the drug. It was a very clean system, because you are reducing the number of excipients you would need to utilize. The big problem here is that it wouldn't dissolve in perfluorodecalin.

Q. **What wouldn't dissolve in perfluorodecalin?**

A. **The brimonidine tartrate. So it was a suspension.**

Q. **So let me stop you right there. What is the difference between a suspension and a solution?**

A. **Well, a suspension has solid particles floating around in the vehicle, in the carrier system, versus the drug, in this case, brimonidine tartrate, being homogeneous, a part of the aqueous system.**

Q. **So you are trying, still, some gels, three different gels. Those are going to be in solution, the brimonidine is going to be in solution in the gels. Is that right?**

A. **That's correct.**

Q. **That is why you are still formulating an acidic pH of 6.4?**

A. **That is correct.**

Q. **Then you are thinking about, well, let's try it in perfluorodecalin?**

A. **Pfd.**

Q. **Let's try it in pfd but as a suspension?**

A. **As a suspension.**

Q. **Let's turn to page 8 of that same document and go to the first three sentences, if we could blow those up. And let's see what the results were of these reformulation efforts. So we have been through 11 in the late '96 time frame. We are now talking about five more in the early '97 time frame.**

Could you read for us what this says and then explain to us what it means?

A. **Just the highlighted portion. Is that correct?**

Q. **Yes, please.**

A. **The reformulations that offered an ocular pharmacokinetic advantage, however, were also cursed with a significant systemic disadvantage.**

Plasma concentrations were consistently higher after Aquasite and both carbopol formulations than after Alphagan, registration mark.

I think that is a /35 microliters. This observation was both unexpected and unwanted, because such a phenomenon in humans will lower the systemic safety margin.

Q. **What is -- we now know what it says. Can you tell us what it means?**

A. **Basically, it's telling you that the drug is being eliminated at such a rate, brimonidine tartrate, that is, that, once instilled, is being eliminated via nasal lacrimal duct, at which point the drug brimonidine tartrate will get absorbed into the bloodstream, and, thereby, have this what is termed here as systemic effect and can cause side effects as a result.**

Q. **I take it that's not a good thing?**

A. **Well, we are not targeting the brimonidine tartrate for the bloodstream in this particular case.**

Q. **What are you targeting it for?**

A. **I am targeting it for the eye, and specifically into the aqueous humor, through the cornea.**

Q. **Now, didn't you hypothesize that by using a gel that the brimonidine would stay on the eye longer, giving it more of an opportunity to be absorbed in the eye rather than end up in the bloodstream?**

A. **I would have predicted that but we had an unexpected result.**

Q. **Do you find the field of formulations always predictable?**

A. **No, far from.**

Q. **Do you find the field of formulations that you always end up with the expected results?**

A. **Only if you are reproducing a study that you have already done how many times. The answer to your question is no. You do have unpredictable results and they do keep happening.**

Q. **In your reformulation efforts of trying to improve Alphagan and make a more, either effective and/or safe brimonidine product, did you find, based on your work, that the results were expected, predictable, and anticipated?**

A. **No, absolutely not.**

Q. **In fact, what did you find?**

A. **The complete opposite.**

Q. **So now we have gone from the 11 formulations in late '96, five more formulations in early '97, let's turn to JTX-035, and go specifically -- sorry, I got ahead of myself. JTX-095, and go to page 3 and blow up "Manufacture of Formulations." Now we are in the mid-1997 time frame. Now we see four more formulations on top of the 16 we have already talked about. Do I have that right?**

A. **Yes.**

Q. **Can you describe for the Court what these formulations are?**

A. **Well, these were prototype formulations, again, formulations that we are still evaluating. There is the Alphagan brimonidine tartrate as our control, .2 percent, and the acidic conditions.**

Q. **Is that the first line, if we could highlight that? That is always the control, whatever formulations you are testing against, you use the Alphagan, the original Alphagan as the control?**

A. **Yes, for studies that involved Alphagan, yes, that it acted as an active control.**

Q. **Now we see for the first time, 17 formulations later, the appearance of Refresh Purite in the formulations. Is that right?**

A. **Yes, that's correct.**

Q. **So the first one says, brimonidine tartrate .2 percent in Refresh Purite, pH 7.4. Did I get that correct?**

A. **You got that correct. The only thing that I would want to highlight, though, we used Refresh Purite as the name because it's understood these were the excipients we were using.**

Q. **So you didn't just take a bottle of Refresh Tears off the shelf and mix some brimonidine in it?**

A. **No, absolutely not. And Refresh Purite is at 7.7 anyway. And you had to adjust the excipients because of tonicity, osmolality to make sure you had an isotonic system for the eye. You don't want too much salt in there, you don't want too little.**

Q. **You said tonicity, osmolality, and isotonic. Can you tell the Court briefly what those three terms mean?**

A. **To put them all together for the Court to understand, it's, whether it be the blood or other biological milieu that you have with the human body that's specific to the eye, you want to have a balance of solids that is kind to the cells and the tissues that make up the eye. In this particular case, the precorneal area, which is a highly sensitive area.**

In order to do that, you want to ensure that the excipients that you are using are in balance with the biological tears, in this particular case, that bathe the eye. And you want to ensure that you don't create an imbalance. If you do, if you have too much salt there, it is going to sting, as would changing pH. If you had too little salt in there, it would also sting.

Q. **Now, we have heard that Refresh Tears, the product itself, was marketed in this time frame now, 1997, and was FDA approved. Why wouldn't you just take a bottle of Refresh Tears, stick the brimonidine in it, and call it a**

glaucoma medication?

A. **There was no data at that point in time for us even to think about adding in an artificial tear. It wouldn't achieve what we were trying to achieve, which was a soluble form of brimonidine tartrate as a physiological pH that had a good bioavailability, good therapeutic effect. And one doesn't go down the path in just selecting -- there is so many artificial tears out there in the marketplace, you would be doing that consistently each and every time.**

Q. **Well, at some point, you did take at least the, I think you described them as the excipients from the Refresh Tears product and combine them with brimonidine tartrate. That is the formulation we are looking at right now?**

A. **That is the formulation. But understand why we are thinking about Refresh Purite at the time, was to name it as Refresh Purite. And, again, you need to balance the salts. You want to make sure the tissue cells have a good influx and de-flux of water. You don't want change that balance, that gradient. That could upset the cells, again, cause some damage.**

But we were interested in the Purite, per se, as a preservative.

Q. **You have told us many times that you have been told that brimonidine tartrate at a higher pH, for example, here, 7.4, is either not going to go into solution, or if it does,**

it's not going to stay in solution. Yet, you are trying this formulation right here.

Why did you do that if you thought it wasn't going to work?

A. **Well, there was work that was being done with Dr. Kerslake, and he had one of his staff, Angel Padilla, who was a professional, a senior professional at the time, we directed him to conduct some studies, formulation studies, which included Purites. We were interested in Purite. Purite was in Refresh Purite, let's also use the excipients and produce a formulation, and we still wanted to target physiological pH.**

Q. **Did you think at this point in time, or did you expect -- let me rephrase that.**

Did you expect, at this point in time, that the brimonidine would remain soluble at that 7.4 pH?

A. **No, not at all. That is completely against what we understood the behavior of brimonidine tartrate, the behavior of the excipients that are being used in this artificial tear. That's the reason why, if you actually go to the formulation below, we actually included a known solubility enhancer, cyclodextrin.**

MS. BROOKS: We are going to talk for a moment about cyclodextrin . Your Honor, I am not sure when you want to do the afternoon break?

THE COURT: How much more direct?

MS. BROOKS: Dr. Olejnik, at this point, I was going to ask to come down and draw cyclodextrin for the Court and explain its mechanism of action. I don't know if this is a good time to break or if you want to do it after that.

THE COURT: Depending upon how much more time you have on direct. But you probably have a substantial amount more time.

MS. BROOKS: I do, Your Honor.

THE COURT: Let's take a short stretch break then.

(Recess taken.)

THE COURT: Please take your seats and let's resume.

MS. BROOKS: Your Honor, with the Court's permission -- can Your Honor see that white board all right? If Dr. Olejnik writes towards the top of it.

THE COURT: Yes.

MS. BROOKS: Thank you. Can Dr. Olejnik step down toward the white board.

(Witness steps down from stand.)

BY MS. BROOKS:

Q. **Sir, right before we broke --**

A. **You want to see my artwork.**

Q. **Yes. Right before we broke, we were talking about how in the third formulation down here, the Refresh -- the brimonidine tartrate .2 percent in Refresh Purite was cyclodextrin, that you deliberately added the cyclodextrin because it was known to enhance solubility, if I understood you correctly?**

A. **That is correct.**

Q. **Now, what was it about cyclodextrin that caused it to enhance the solubility of, for example, something like brimonidine. Could you explain it to us graphically?**

A. **There will be a little bit of words as to how I think I am going to draw this thing.**

THE COURT: Do you want to move so you can see, counsel?

MR. BOGGS: May I.

THE COURT: Yes.

BY MS. BROOKS:

Q. **You need to keep your voice up, Dr. Olejnik, so the court reporters can hear you.**

A. **I tend to have a loud enough voice.**

The cyclodextrin is a known solubilizing agent, it is well-known in the field. It is used to increase the solubility of those compounds that are in a non-ionized insoluble form normally in water.

One of the things that cyclodextrin possesses as

its inherent properties -- and there are a variety of cyclodextrins, it depends on the -- it's a ring circular of basically sugars, if you will, and it can be in five, six, seven sequences, and they are denoted alpha, beta, gamma. I do apologize to Your Honor and to the Court for my artwork.

Basically, it is a cyclical ring of various sugars attached. As it's in the system in solution, you think of it as a cylinder. So this sugar ring, if you will, exists all around here, and so on and so forth.

What is interesting about the excipient, about the cyclodextrins, is that the hydrophilic portions, the O-H groups, it's more in a 2-D, not a 3-D, so apologies, exist on the outside. Inside is predominantly what's called the hydrophobic core. It is where it attracts oil-loving compounds. It's like attracts like.

So for a drug that is non-ionized, more lipophilic, more oily, it has a preferential affinity for it to reside inside the core of this cyclodextrin. Think of it also as a donut, essentially. It will fit inside.

The outside of the ring is predominantly hydrophilic. It exists bathed in the water phase.

So what happens is the drug that is insoluble, non-ionized, lipophilic, has an affinity to reside inside this cylindrical core. And the overall cyclodextrin is protecting it to the aqueous phase, it looks as if the drug

is in solution.

So it's basically what a cyclodextrin is. There are more, obviously, other chemical facets to it. But that's essentially what cyclodextrin does.

Q. **Thank you, Dr. Olejnik.**

(Witness resumes stand.)

BY MS. BROOKS:

Q. **We are going to come back to the exhibit that is presently up there. Let's just go for one moment to JTX-002, that is the '873 patent, and specifically to Claim 1. That would be at Column 17.**

There, you are talking about in that claim a solubility enhancing component other than a cyclodextrin.

Did I read that correctly?

A. **That is where?**

Q. **If you look up, perhaps we could highlight it, it's the second element. A solubility enhancing component --**

A. **Yes, I see that.**

Q. **-- other than a cyclodextrin.**

So, in this particular patent, in the claim, it specifically excludes what you have just drawn for us, the cyclodextrin, as being the solubility enhancing component of your invention?

A. **That's correct.**

Q. **Is that correct?**

A. **That's correct.**

Q. **And at the time that you were doing the work that resulted in the four patents at issue, was it already known that cyclodextrins operated in this fashion?**

A. **Yes.**

Q. **Now, if we could go back to what we had on the screen, which was JTX-095, and the formulations, eventually -- I am just going to skip ahead for one second in time, Dr. Olejnik -- eventually, you would come to discover that carboxymethylcellulose, or CMC, was actually acting in these formulations to enhance the solubility of brimonidine. Is that right?**

A. **Yes. We observed that effect, yes.**

Q. **Was there anything in the makeup of carboxymethylcellulose that would lead you to believe that it would act like cyclodextrin in this tubular fashion?**

A. **No. CMC doesn't exist in that state at all.**

Q. **So is there anything in your prior work or knowledge that would lead you to believe that in having CMC, or carboxymethylcellulose, as part of the eventual formulation, you would be getting a solubility enhancer of the brimonidine?**

A. **Not from CMC.**

MR. BREISBLATT: Objection. Leading.

THE COURT: It is leading.

MS. BROOKS: I apologize, Your Honor.

BY MS. BROOKS:

Q. **Did you believe, based on all your work, did you or did you not believe, based on all your work, at the time of the inventions, that carboxymethylcellulose would act to enhance the solubility of brimonidine?**

A. **No.**

Q. **Now, if you knew, though, that cyclodextrin worked as a solubility enhancer, why didn't you just start right away with the second formulation there -- the Refresh Purite, if we could highlight it again, with cyclodextrin -- why didn't you just start your reformulation efforts right there with that?**

A. **Well, there were certain concerns that we had over the use of cyclodextrins. It is not to say that they don't have utility. They do. Cyclodextrins have never been used in a product that I was aware of in the eye. There are also concerns that the fact that you are able to solubilize the drug in that center core, if you will, and as I alluded to earlier, with regards to when you put a drop in the eye, with the blink reflex, and all the other activities that go on, to remove what is essentially a foreign substance being thrown into the eye, again, mother nature is very adept at eliminating stuff out of the eye, there was a concern that by having the brimonidine tartrate inside the cyclodextrin**

core, that as things are going extremely fast, would there be sufficient time for the drug to be released out of the hydrophobic core, to then go and have an effect in penetrating through the cornea, and then on into the eye itself, to have a therapeutic pharmacological effect in lowering intraocular pressure.

So there was a concern over the fact that as much as we have achieved a solution, if you will, there was a concern that that may actually work against us, because the drug would not be bioavailable to the sufficient level that we were trying to achieve.

Then, as we understand about cyclodextrins, and some of these have, again, depending on concentration, nephrotoxicity effects that can impact the kidney. So there were some safety aspects surrounding the choice of that excipient.

Q. **If, in fact, the cyclodextrin had ended up making the brimonidine less bioavailable, meaning less of the brimonidine got into the eye and more of it got into the tear system, then what would happen to the brimonidine? Where would it go?**

A. **It would go into the bloodstream, be absorbed. And you would have a systemic effect that were described, I think, by that David Small paper.**

Q. **Again, is that a good or bad thing?**

A. **No, it is not something you would want. I know the risk-benefit. But clearly, in this particular case, it is something you would want to avoid.**

Q. **Now, you have already, though -- not already, you have now, 17 formulations later, do have a formulation that has brimonidine tartrate .2 percent in Refresh Purite with a pH of 7.4. That is the one right above the one that is highlighted. If we could highlight that one.**

Why haven't you then just finally settled on this one? Why do you have yet another formulation that involves a gel, Smart Hydra Gel, and another formulation that involves Castor Oil?

A. **Well, we were evaluating -- we weren't just satisfied with putting a drug in excipients in Refresh Purite. Again, there were questions over whether that would work or not. There was nothing that would lead us towards that conclusion. It was important for us to evaluate other systems.**

There was some interesting gel technology that was going on at MIT. And that was, I don't fully recall, I think it was a spinoff company, it was part of the university, I don't exactly recall, but they were called gel sciences. And they had some very interesting polymer systems that could enable us to achieve our goal. So we were evaluating that system.

Then there was the Castor Oil emulsion, because we were developing Restasis, although it wasn't called Restasis at this time, this is the cyclosporin product that Allergan has and the treatment of dry eye, understanding artificial tears are palliative, they are not symptomatic, they are not just addressing the underlying disease, but we were dealing with cyclosporin, which is an extremely hydrophobic compound. So we already had a solubility issue right from the get-go.

We were looking at technologies there, could we enhance the solubility of the cyclosporin. And the Castor Oil emulsion, which ultimately became the system of choice and became Restasis as a product with the cyclosporin compound, a treatment of dry eye, we looked at the emulsion system as well.

Well, if it is going to work for cyclosporin, let's look and evaluate for brimonidine tartrate.

Q. **So this is now the mid-1997, where, if I am understanding this correctly, you still have not settled on putting the brimonidine or using the brimonidine with Refresh Purite at 7.4 percent. You are still looking at yet other formulations?**

A. **We are still evaluating these prototype formulations. They are not the final formulations. We are still doing a full assessment.**

Q. **And the Castor Oil, is that a solution or is that a suspension or is that an emulsion? And if there is a difference?**

A. **It's an oil in water emulsion. It's basically very small, micro sized globules of oil, discrete globules of oil that are in what's called the continuous phase, which is water.**

And it's at a pH, although there isn't a pH here, it is at a pH around 7.3-7.4. The reason there is no pH assigned here because what if you deal with an emulsion and you are doing a pH measurement, the actual oil globules, they will have an affinity for the glass probe or the pH probe, and it causes the number, the pH to vary considerably. So it is difficult to do an actual measurement with the oil present. But if you took the oil out and looked at the aqueous system itself, it would have a pH in that same order.

Q. **Now, the last formulation, the Castor Oil emulsion, actually, that doesn't have Purite in it, I take it?**

A. **No, it does not.**

Q. **And the one before that, the Gel Science Smart Hydrogel, that doesn't have Purite in it?**

A. **No, it does not.**

Q. **But the Refresh Purite formulation with and without the cyclodextrin, those actually have Purite?**

A. **Yes, they do.**

Q. **And what is Purite?**

A. **Well, Purite is an oxychloro complex that has been found to be an effective preservative agent.**

Q. **Do you know what the preservative was in original Alphagan?**

A. **It was benzochlorine chloride, BAK.**

Q. **Is that a fairly common preservative in ophthalmic?**

A. **It's ubiquitous. It is used considerably in the ophthalmic field. It has its own issues associated with it, but, overall, it's a good conservative system recognizing that the activity of a preservative is to essentially kill cells. In this particular case, microorganisms. So you have got to get a fine balance between killing the bacteria that once upon opening the bottle, there is always the potential for contamination, a microorganism entering into the container closure system, there is a necessity to be sure that if microorganisms get in, they get killed. But you don't want to have a deleterious impact on the actual artificial cells themselves. So there is a finite balance, which is why we are very careful in the selection of the concentration of the preservative that goes into an ophthalmic product.**

Q. **In this particular formulation where it has the Refresh Purite, is the Purite going to be in lieu of the**

BAK?

A. **It is.**

Q. **Did you have any concerns at this point in time as to how Purite might interact with the brimonidine?**

A. **We did.**

Q. **What were those concerns?**

A. **Purite, it's mode of action, it is an oxidizing agent. And one of the things that any formulator would know, that the presence of an oxidizing agent on a compound that is susceptible to oxidation, there would be an issue over the actual drug compound. It would degrade, and it could degrade rapidly.**

Q. **If it degraded, if the Purite degraded the active, the drug compound, then what would happen to the medication itself?**

A. **Well, your potency diminishes, drops. And you will not have a therapeutically effective product at the end of the day.**

Q. **Up until this point in time, we are talking about the mid-1997 now, had Purite, to your knowledge, been used as a preservative with an active ingredient, combined in the formulation?**

A. **No. No.**

Q. **So was this going to be a first?**

A. **This would be a first.**

Q. **Now, if you could turn to JTX-035 in your binder.**

If we could go to the second page of the memorandum. Down at the bottom, it says, Minutes from August 13, 1997, Team Meeting. Correction.

Can you read to us what that says and then explain to us what it means?

A. **Can you repeat that again, please?**

Q. **Sure. If we can just highlight where it says, Minutes from August 13, 1997, Team Meeting, if we could highlight the three lines that are underneath it, could you explain to us -- first of all, could you read to us what it says and then explain to us what it means?**

A. **"The formulation needs to be above pH 6.8 in order to minimize oxidation. The formulation has a pH of 7.4. In-lab stability available for ten days at 60 degrees, in parentheses, 98 percent, with 100 ppm Purite."**

That means parts per million, "ppm."

Q. **What does this mean? Why does the formulation have to be above a pH of 6.8 in order to minimize oxidation? What is the concern this is addressing here?**

A. **The concern is, if you are looking at a very low pH, the Purite itself degrades. So you want to maximize the stability of the Purite. And stability is increased as the pH is increased. So in order to ensure that, one, you have the Purite stable enough, by having it stable at a higher**

pH, the thinking was that we would reduce the impact, oxidizing impact on the drug itself.

So there was a two for one sort of thing out of this evaluation. One, stabilizing the Purite, but also looking to address the stabilization of the brimonidine tartrate.

Q. Let's fast-forward, then, to 1998, and then go to JTX-054 in your binder. If we could blow up the first part, the "To," the "From," the "Subject," the date. Who is Hans Peter Pfleger? JTX-054. It should be close to the end of your binder. Hopefully, you are not missing it. If you are, we can share on the screen.

MS. BROOKS: Your Honor, might I approach the witness to help?

THE COURT: Sure.

MS. BROOKS: Thank you.

Your Honor, does the Court's binder have it, might I inquire? My binder does.

THE COURT: The last page, the page ending in 976?

MR. BREISBLATT: We have it.

MS. BROOKS: Yes, Your Honor. For some reason, Dr. Olejnik is the only one that doesn't. So I am going to hand you my copy, Dr. Olejnik.

(Court hands document to witness.)

MS. BROOKS: Oh, thank you, Your Honor.

THE WITNESS: Thank you, Your Honor.

BY MS. BROOKS:

Q. **Dr. Olejnik, who is Hans Peter Pfleger?**

A. **Hans Peter Pfleger is in marketing at Allergan.**

Q. **Who is Ed Kerslake and Orest Olejnik?**

A. **Dr. Edward Kerslake, he was my collaborator, formulator, working in my organization. Orest Olejnik, that is me.**

Q. **The subject here is Alphagan reformulation. Is that right?**

A. **That's correct.**

Q. **The date is now June 9th, 1998?**

A. **Yes.**

Q. **So you have been working on this for about a year and a half, this project?**

A. **At least.**

Q. **If we could go to the second page of the memo, and specifically the third page of the memorandum and blow up that paragraph. It says, "Despite the observed, bioavailability improvements of brimonidine Purite .2 percent from animal pharmokinetic studies, this was not reflected in the human Phase 2 studies."**

Did I read that correctly?

A. **Yes, you did.**

Q. **It says, "Based on this data, alternative formulations are unlikely to offer any appreciable benefits to the efficacy/safety profile of Alphagan."**

Did I read that correctly?

A. **That is correct.**

Q. **What did that mean?**

A. **Well, in all the systems formulations that we had considered, and there is an abundant number of them, the data indicated that we are not going to achieve anything that is better than the existing Alphagan product.**

Q. **And this is in 1998, that this is being said?**

A. **That's correct.**

Q. **Now, you weren't present in court with Dr. Whitcup testified, but I will represent to you, Dr. Olejnik --**

MR. BREISBLATT: Objection. Form of the question.

THE COURT: Well, counsel, it's a Bench trial. Continue.

BY MS. BROOKS:

Q. **Dr. Olejnik, I will represent to you that Dr. Whitcup has testified that there actually turned out to be increased safety profile of Alphagan P over Alphagan. Are you aware of that to be a fact?**

A. **I am aware of that, yes.**

Q. **So this statement here turned out not to be accurate.**

Is that right?

A. **That's correct. It's contrary to the outcome.**

Q. **But, in fact, back in 1998, this is what you believed?**

A. **Yes.**

Q. **In fact, did anyone else also believe it? If you can read the next line that's not highlighted. "This was consistent with the assessment and predictions submitted by an external advisory panel of experts."**

What's that talking about?

A. **We had brought in a number of key opinion leaders, experts in the field, to review the data we had, to assess our formulations, our strategies, and so on. And we were seeking their advice and input and guidance.**

Q. **Did your formulation efforts at that point of the brimonidine tartrate in combination with the Refresh Purite, did that meet with skepticism?**

A. **Would you repeat the question again?**

Q. **Did your formulation efforts at this point in time, which is now moved all the way up to '98, where you now finally have combined the brimonidine Purite -- excuse me, the brimonidine with the Refresh Purite, did that combination, as far as it being more effective than original Alphagan, did that meet with skepticism?**

MR. BREISBLATT: Objection. Leading.

THE COURT: Well, it is. And maybe a little

vague. Maybe you could reformulate the question.

MS. BROOKS: Reformulate my question, Your Honor.

BY MS. BROOKS:

Q. **Dr. Olejnik, what if anything were you being told by outside experts as to whether or not a formulation containing brimonidine and Refresh Purite was going to have an increased efficacy or safety profile over original Alphagan?**

MR. BREISBLATT: Objection. Hearsay.

THE COURT: Yes. I am going to sustain that objection.

MS. BROOKS: Your Honor, again, I was offering it because, once again, it turns out what they were saying wasn't true and there was indeed an increased safety profile.

MR. BREISBLATT: She is offering it for the truth of the statement at the time.

THE COURT: Aren't you?

MS. BROOKS: It turns out the statement wasn't true, no. I am offering it to show the skepticism of the industry at the time.

THE COURT: I will allow it. Go ahead.

BY MS. BROOKS:

Q. **Dr. Olejnik, do you remember the question, because I**

think I forgot it?

A. **Well, I will be kind. I won't ask you to repeat it. Hopefully, I will answer in addressing your question.**

When we had the experts and we presented all this data to them, as they assessed it and evaluated it, they said, You are barking up the wrong tree. You are going to have to go to a very sophisticated system to achieve what you want to achieve.

Q. **And, in fact, it talks about a controlled ocular delivery insert in the next sentence?**

A. **Yes, it does.**

Q. **Did you, however, you, the formulators, continue to move forward with your attempts to develop a reformulation of Alphagan that was going to have either an enhanced efficacy or enhanced safety profile?**

A. **Yes. We would still continue the prototype formulation development, gather more information, to go down the path of a controlled ocular delivery insert, where you are looking at a different time profile, very different systems, very sophisticated, manufacturing costs, et cetera. I think that would not be a benefit to the patient at the end of the day just based on the costs of producing such a product.**

Q. **Now, we know, because we have already heard testimony**

from Dr. Whitcup, that eventually Allergan did, in fact, get FDA approval for a drug called Alphagan P?

THE COURT: Ms. Brooks, probably it is not necessary, with this witness, to say things like, We know because we heard from Dr. Whitcup, I think that's improper.

MS. BROOKS: Thank you, Your Honor.

BY MS. BROOKS:

Q. **Let's just fast-forward. Do you know what Alphagan P is?**

A. **Yes, I do.**

Q. **What is Alphagan P?**

A. **It's brimonidine tartrate at .15 percent.**

Q. **What is the pH of Alphagan P?**

A. **It's at 7.2 is the target pH.**

Q. **I believe you told us that you had been told that brimonidine wouldn't be soluble at a higher pH?**

MR. BREISBLATT: Objection. Leading.

THE COURT: Well, overruled.

MS. BROOKS: Just foundation, Your Honor.

BY MS. BROOKS:

Q. **Did you believe that brimonidine, before all of these efforts, wouldn't be soluble at that pH of 7.2?**

A. **Yes, we knew there were solubility challenges, yes.**

Q. **Did you find that, in fact, that was not the case in this particular formulation?**

A. **No. The brimonidine tartrate was in solution.**

Q. **Now, if we could go, please, to the '210 patent, and specifically Figure 1 of the '210 patent. Dr. Olejnik, that is JTX- --**

MS. BROOKS: Your Honor, would the Court like your notebook back?

THE COURT: Yes. I was just wondering where it went.

THE WITNESS: Sorry, Your Honor.

BY MS. BROOKS:

Q. **Dr. Olejnik, what are we looking at here?**

A. **Now, which was the JTX?**

Q. **The '210 patent, JTX-003?**

A. **Okay.**

Q. **Figure 1. What are we looking at here?**

A. **We are looking at the solubility of brimonidine tartrate, which is on the y axis, y axis, and on the x axis below, horizontal axis, that is the pH.**

So we are looking at the solubility profile of brimonidine tartrate with pH and its influence by CMC, the legend up above in the top right quadrant, the CMC is the carboxymethylcellulose, and they are designated at different concentrations, and the signs are associated, representing concentrations across at the top, representing percent, CMC in a circle, 0.058 percent, and so on.

Q. **Let me ask you this: Was carboxymethylcellulose in the original Alphagan formulation?**

A. **No, it was not.**

Q. **How did it come to be in the Alphagan P formulation?**

A. **Again, we were evaluating the brimonidine tartrate in looking at the utilization of the Purite preservative. And we decided that we would essentially take the excipients that were being used in Refresh Purite and use that range of excipients in the formulation of the .15 percent or the new formulation, reformulation of brimonidine tartrate.**

Q. **And in doing so, did you discover something about carboxymethylcellulose and its effect on the solubility of brimonidine?**

A. **We saw some unusual event that was, in our minds, very surprising.**

Q. **Can you tell the Court, please, what you saw?**

A. **What we saw was the effect, apparent effect of the CMC enhancing the solubility of brimonidine tartrate at a higher pH.**

Q. **Was the CMC enhancing the solubility of brimonidine at a higher pH, was that result expected by you?**

A. **Absolutely not. That was a surprise event for us.**

Q. **As a result of that -- let me ask you this: Was that data that reflected CMC enhancing the solubility of brimonidine at higher pH's, was that data reflected in the**

patents at issue?

A. **Yes.**

Q. **And the chart we are looking at here, Figure 1, does that reflect that data?**

A. **That reflects that data, yes.**

Q. **By having carboxymethylcellulose enhance the brimonidine at higher -- the solubility of brimonidine at higher pH's, did that enable you now, then, to formulate brimonidine at the higher pH's without it falling out of solution?**

A. **Being able to now have the brimonidine tartrate in solution at a more physiological pH, the answer is yes, in the presence of CMC.**

Q. **Now, you have mentioned several times throughout your testimony the term "bioavailability."**

Can you tell the Court what "bioavailability" means?

A. **In the simplest form, it's, again, making the drug available to the biological system, to then have an appropriate effect.**

Q. **Is there such a thing as something called the pH partition theory?**

A. **Yes, there is.**

Q. **Does that relate in any way to bioavailability?**

A. **Yes.**

Q. **In what way does the pH partition theory relate to bioavailability?**

A. **Well, the pH partition is where you have a higher lipophilic moiety of the drug and you can control it by changing the pH. You can increase the non-ionized form of the drug, which will have a higher lipophilic oil characteristic. And it will reside more in the oil phase, and biological membranes are composed of phospholipids, yes, they are a mix of aqueous lipid systems. But having, adjusting the pH, you can actually adjust the partitioning of the drug as an outcome of pH.**

Q. **Do you have an animation that would demonstrate to the Court what you are talking about, where you change the amount of ionized versus unionized in the compound?**

A. **Yes, I do. It's a little improved upon my artwork. But I do have a large though simple schematic.**

Q. **If we could play that, please, and as we are playing it, Dr. Olejnik, if you could explain to the Court what the Court is looking at?**

A. **The Court is looking at the surface of the cornea.**

Q. **Could we freeze it there?**

A. **The cornea is highly lipophilic.**

Q. **What does that mean, to be lipophilic?**

A. **It's oily, waxy. It's a little exaggeration on the waxy. It's an oily film. And in order for it to ensure**

bioavailability and ensure maximum penetration of the drug, you first and foremost want the drug to be in solution, and, preferably, in a non-ionized state, meaning the non-ionized form is more lipophilic than the ionized form, because under the conditions in the eye, you want the non-ionized, which is lipophilic, to have an affinity for the lipophilic cornea.

So, again, it's like with like. Oil to oil. So the non-ionized form is more oily, the epithelium layer of the cornea is oily. There is a propensity for the non-ionized to have some affinity for the cornea.

Q. **You mentioned at the beginning of your testimony something called pKa of the drug.**

How, if at all, does that relate to this?

A. **Again, the pKa, you understand that with the pKa, it will tell you the ionization aspects of the drug. So you will know how to manipulate the pH, if you will, to achieve a higher non-ionized state. In the case of brimonidine tartrate, the higher the pH is, the more non-ionized form you are going to have.**

However, the characteristics of the non-ionized form of brimonidine is such that it is insoluble, which is why we went down the path of developing a formulation and discovering a formulation that enhanced solubility of the brimonidine in a more non-ionized state.

So what we are seeing here, in a very schematic representation, the red represent the ionized moieties of the drug versus the yellow, which is more -- more of the -- versus the yellow, which is a non-ionized form, versus the red, which is the ionized form. And more of the non-ionized form, lipophilic form, penetrate through the cornea.

That isn't to say that some of the ionized form will not enter through the cornea. It still does.

Q. **Did we just see a demonstration, then, of changing where it's 50-50, you are at the pKa of the drug, there is half that are ionized and half unionized, by formulating at a higher pH, do you then end up with more of the unionized?**

A. **You will have more of the unionized and a high propensity for more of the drug to penetrate through to the eye.**

Q. **By having more of the drug penetrate through to the eye, what does that, if anything, do for you?**

A. **Well, that allows us to now think about, sometimes more is not always better. And by that, I mean, knowing that we could get more drug into the aqueous humor, we still wanted to be mindful of side effects, systemic effects, what have you, but particularly any effect in putting too much drug into the eye. It allowed us to reduce the amount of brimonidine tartrate, lower the concentration, but yet achieve a certain equivalency to the original Alphagan, the**

.2 percent.

So it allowed us to manipulate the amount of drug we would be presenting to the eye because we knew that we could increase the penetration, due to the non-ionized form, lower the concentration, still achieve the therapeutic effect, but diminish any potential side effects, systemic effects due to wash out.

Q. **So you have just described for us over the course of all these formulation efforts, it sounds like several discoveries that you made. Did you apply to the United States Patent Office for patent protection for those discoveries?**

A. **Edward and I did, yes.**

Q. **If you would look at JTX-008, is this a declaration that you filed on behalf of the first application, patent application, that you filed with the United States Patent and Trademark Office?**

A. **Yes, it is.**

Q. **And if we could go specifically to Paragraph 7. Actually, let me back up.**

If we look at Paragraph 4, here you are talking something about the Burke patent. Is that right?

A. **That's correct, yes.**

Q. **If we go to Paragraph 5, you are talking about something called Remington?**

A. **That's correct.**

Q. **Had the original claims as filed with the U.S. Patent Office been rejected as being obvious over Burke and Remington?**

A. **I believe, yes.**

Q. **So did you file a declaration to explain to the examiner why what you and Dr. Kerslake had discovered was, indeed, different and new and novel over Burke and Remington?**

A. **Yes. I felt it important to ensure that it was fully understood about the observed effects.**

Q. **If we could look at Paragraph 7, please. Can you tell us, please, in Paragraph 7, what it is that you are telling the U.S. Patent and Trademark Office in this paragraph?**

A. **Well, I am telling that the CMC at the concentrations we were considering were very different in behavior to the other listed polymers. And the reason behind that was not just because of the solubility enhancement of the CMC that we unexpectedly observed, surprisingly observed, but the fact that when you are dealing with the eye, which, again, has good blink rates, the resonance time of products in the eye are very, very short, we are still observing a heightened amount of drug that is in the aqueous humor. That was borne out of the studies that were conducted through the pharmacokinetic group and there is data there**

that have indicated that we were getting fairly substantial concentrations of the brimonidine tartrate into the aqueous humor.

And why is that?

Well, there is the solubility effect. There is the pH. But it was also the fact that what was surprising, and the other thing to also know about the cornea and the eye, it is negatively charged. That is contributed by new things that are negatively charged. CMC, being a polyanion, is negatively charged. And you think of it akin to putting the North Pole of the magnet with the North Pole of your -- another magnet and trying to push them together, they will repel.

Those are dipole-dipole reactions. But they basically illustrate the point that negative charge to negative charge will repel.

So you would expect that the CMC not to reside on the eye long enough and thereby causing the washout of the system to be increased. We didn't see that from the pharmacokinetic studies. I know there are mucoadhesive studies that have been performed elsewhere. That is a different story. We can spend many an hour on discussions of those.

Q. **That's okay.**

A. **But the CMC in this particular case, the**

concentrations we were looking at, there is quite a lot of papers out there, also, showing that certain polymers don't adhere, there is also an interesting -- knowledge through Caufield out of Bristol University, has done a lot of work on mucin technology --

MR. BREISBLATT: Your Honor, I think we are off the course.

THE COURT: What happens here is a little different than what happens in the classroom or the lab. There are rules. He makes a proper objection. I am going to sustain it.

BY MS. BROOKS:

Q. **Dr. Olejnik, I know the subject is near and dear to your heart, but just to cut to the chase here, when you say to the Patent Office about three-quarters of the way down or two-thirds of the way down, "This surprising result may be due to the repulsive forces between the polymer and the cornea orienting the hydrophilic portions of the molecule away from the cornea, thus permitting the hydrophobic domains of these polymers to form an interaction with the lipid portion of the cell surface," are you essentially -- what are you, in five sentences or less, telling the Patent Office there?**

A. **What I am telling the Patent Office is that the CMC is rearranging itself because of the negative charge,**

repelling, there must be a different orientation of the polymer.

Q. **When we go up to, I believe it's the third sentence, "I have discovered as a result of work done and/or directed by me at Allergan, that CMC possesses the surprising advantages of both increasing the solubility of brimonidine in solution as shown in Table 1 and causing such solutions to have superior adherence to cell surfaces, including ocular surfaces such as the cornea."**

Is that what you have just been describing to us over the course of the last hour and a half?

A. **Yes.**

Q. **Did you believe that when you said it to the U.S. Patent and Trademark Office?**

A. **I believed it then. I believe it now.**

Q. **And after you filed this declaration, did, in fact, the first of the four patents issue?**

A. **It did.**

Q. **And did later, then, the additional three?**

A. **Yes.**

MS. BROOKS: Thank you very much, Dr. Olejnik. No further questions, Your Honor.

THE COURT: Thank you, counsel. Mr. Boggs, you may cross-examine, sir.

MS. BROOKS: I hate to ask this, Your Honor, but

could we have a copy.

THE COURT: I imagine you could.

MS. BROOKS: Thank you. I hesitate to ask, but...

MR. BOGGS: The logistics are a little rough today, Your Honor. I apologize.

CROSS-EXAMINATION.

BY MR. BOGGS:

Q. Hello, Dr. Olejnik. How are you?

A. Very well, Mr. Boggs.

Q. Good.

Just a few moments ago, you were talking about Remington. What is Remington?

A. Remington is one of a number --

MR. BENSON: Your Honor, could we have a copy? I request a copy of the exhibits as well.

BY MR. BOGGS:

Q. Remington?

A. Remington Sciences is one of many reference books, there is Martindale, there is others, that talk about ingredients, excipient's information about compounds, basically a general reference book that one normally goes to.

Q. And is Remington one of those standard reference books for pharmaceutical formulators?

A. **It's one of the references that is used. I know here in the U.S. it is used considerably. I have used it in the U.K. My preference is Martindale. But they are all one and the same at the end of the day.**

Q. **And they have a lot of the same similar information in them?**

A. **They have similar information. There is different information. Again, it's not holding just to one reference, general reference source. It just provides certain guidance to formulators in the pharmaceutical sciences field.**

Q. **Go ahead and open your book there. The very first, we probably should have done this a different way, but the very first exhibit there, Joint Exhibit No. 9, that is the file history for the '834 patent. There should be a green tab in there. I would like you to turn to the declaration that you signed when you filed the patent application, Doctor.**

I would like you to turn to the declaration that you signed when you filed the patent application.

A. **Where is that, sir?**

MR. BOGGS: May I approach and help.

THE COURT: Please do. You have leave to approach freely, Mr. Boggs.

MR. BOGGS: Thank you.

THE COURT: It is on the screen, too.

THE WITNESS: Yes, I can read the screen.

BY MR. BOGGS:

Q. **This is the patent application, or the declaration for the patent application that you signed. Is that right?**

A. **Well, I don't see my signature. There it is. Yes, that's correct.**

Q. **Okay. Over your career at Allergan, you signed a number of these?**

A. **I have signed a number of these declarations, yes.**

Q. **And you did, in fact, sign this one, you recognize your signature. Is that right?**

A. **That is my signature above Edwards, yes.**

Q. **When you signed this declaration, you said that you had reviewed and understand the contents of the patent application. Is that right?**

A. **That is correct.**

Q. **And you also said that you had read the claims. Is that right?**

A. **That is correct.**

Q. **And at the time, you gained an understanding of the claims. Is that right?**

A. **At that time, yes.**

Q. **Can you flip to the original claims. I believe, if you can find the patent application in there, they start on Page 33.**

A. **This is which tab?**

Q. **If you look at the Bates numbers on the bottom, it's AGN 0226194. It's still Joint Exhibit 9.**

A. **Okay.**

Q. **You have them in front of you now?**

A. **Yes, I do.**

Q. **Now, these are the claims that you filed with your patent application and these are the claims that you indicated in your declaration that you understood. Is that right?**

A. **At that time, yes.**

Q. **Now, this Claim No. 1, if we can highlight that, that claim is not directed specifically to brimonidine tartrate, is it?**

A. **It's directed to an alpha-2-adrenergic agonist.**

Q. **So that is a family of compounds. Is that right?**

A. **It's a family of compounds, class of compounds, yes.**

Q. **Okay. And can you look in your book there for the Small article. Are you familiar with the Small article?**

A. **David Small had a number of articles.**

Q. **There is only one in that book. It's BDTX-166. Do you have that in front of you?**

A. **I have that in front of me.**

Q. **That article is entitled, "Influence of pH and buffer concentration on occular bioavailability of ophthalmic AGN 191103...."**

Do you see that?

A. **Yes, I do.**

Q. **Do you recall this article?**

A. **I remember seeing the article, yes. I don't know when.**

Q. **Could you tell from looking at the article when the date is?**

A. **Well, it was received at the International Journal of Pharmaceutics on the 29th of May, 1996. It was revised a couple of times and then was published in the shortened version, the IJ Pharm in 1997.**

Q. **Now, David Small, you mentioned him earlier, I believe. Who is he?**

A. **He was one of the pharmacokineticists at Allergan at the time.**

Q. **He was on the brimonidine X team. Is that right?**

A. **I believe so, but I would have to go back and check.**

Q. **Now, who are the other authors on this paper?**

A. **There is a Maria Dais. I don't know who she is. There is a Michelle Wong and a Diane Tang-Liu. I know Michelle Wong and Diane Tang-Liu, at the time, they were at Allergan, Diane Tang-Liu, Dr. Tang-Liu is still at Allergan. I don't know about Maria Dais.**

Q. **What is AGN 191103?**

A. **It was another compound that Allergan was studying at**

the time. It had therapeutic effect, some pharmacologic effect on lowering intraocular pressure.

Q. **It was an alpha-2-adrenergic agonist. Is that correct?**

A. **It was an alpha-2.**

Q. **And it is a member of the alpha-2 family. Right?**

A. **It falls into that class, yes.**

Q. **And, structurally, it differs from brimonidine by only one substituent. Is that right?**

A. **Well, it differs by a methyl group versus a bromine group.**

Q. **If you look at Page 197 of the article, which is EDTX-166, the bottom page in the left column, that is the structure for AGN 191103. Is that right?**

A. **That's correct.**

Q. **And the methyl group that you just referred to is that CH-3 group at the middle off the middle of the ring. Is that correct?**

A. **Correct.**

Q. **Now, in the case of brimonidine, is it correct to say that that methyl group is substituted with a Bromo group?**

A. **It's a bromine.**

Q. **So, structurally, that is the only difference. Is that right?**

A. **It's a significant difference. But that is the**

difference from a CH-3 to a Br, yes.

Q. **Structurally, it's the only difference?**

A. **Yes.**

Q. **Now, when you filed your patent application, and we have seen the claims, the original claims, you intended to embrace AGN 191103 when you filed your patent application which led to the '834 patent. Isn't that right?**

A. **It's embracing the family of the alpha-2-adrenergic agonists.**

Q. **And AGN 191103 is a member of that family. Right?**

A. **That would fall under that umbrella.**

Q. **What does the designation "AGN" stand for?**

A. **It's just short for Allergan.**

Q. **So this was an Allergan compound. Is that right?**

A. **It would have been owned by Allergan. We haven't licensed compounds where we do designate an AGN number.**

Q. **And it was being worked with by Allergan scientists. Is that right?**

A. **Yes.**

Q. **Including a scientist who was a member of the brimonidine X team. Is that right?**

A. **Again, if David Small was on the team, then he would have been associated with this compound.**

Q. **And David Small and his co-authors reported to the world the results from this compound before you filed your**

patent application. Is that right?

A. **I don't know. I would have to go back and check.**

Q. **What was the date on the article?**

A. **That was '97, 1997. You are referring to the patent being 2000, whatever that was. Is that what you are referring to?**

Q. **Yes.**

A. **Under that circumstance, yes.**

Q. **Did you ever submit the small article to the examiner for his consideration during prosecution of the '834 patent?**

A. **I don't remember. I would have to go back and check.**

Q. **Did you, yourself, ever work with AGN 191103?**

A. **I don't remember specifically on this compound. I know I was aware of it.**

Q. **You were aware of it?**

A. **I was aware of the 103, yes.**

Q. **In fact, one of those internal memorandums you just finished testifying about referred to AGN 191103. Do you recall that?**

A. **Could you repeat that again, please?**

Q. **One of the internal Allergan memoranda that you just testified about referred to AGN 191103. Is that right?**

A. **Yes. Yes, it did.**

Q. **I would like you to look in the book that Ms. Brooks gave you before and look at JTX-095. Do you see that?**

A. **Yes.**

Q. **Look at the first page of it, if you would. Do you see that it was written by David Small?**

A. **Yes, D. Small.**

Q. **Who was it reviewed by?**

A. **By a Joel Usansky and Edward Kerslake.**

Q. **Edward Kerslake?**

A. **That's correct.**

Q. **And he is your co-inventor on the '834 patent. Is that right?**

A. **He is, indeed.**

Q. **Now, what is the date on this internal memorandum? Let me try to help you a little bit. Can you tell from the dates next to the signatures by the author or the reviewer about the time when the memorandum was written?**

A. **It's in March of '98.**

Q. **And that, too, was before you filed your patent application. Is that right?**

A. **Yes.**

Q. **I would like you to look at Page 7 of 12, if you would. That is AGN 0064123. Look at the last paragraph of text before the references.**

Do you see any reference to AGN 191103?

A. **Yes, towards the bottom.**

Q. **Okay. Okay. That sentence says, "A previous invitro**

assessment of the effect of pH on corneal penetrations of brimonidine showed no influence, but invivo experiments with a closely related compound, AGN 191103, showed substantial improvement in ocular bioavailability with increasing pH."

Do you see that?

A. **Yes, I do.**

Q. **"Although there are physicochemical differences between brimonidine and AGN 191103 that may attenuate the effect of increasing formulation pH on brimonidine's ocular penetration, theoretical considerations and previous experience with AGN 191103 strongly suggest that increasing pH may have a positive effect on life rabbits."**

Do you see that?

A. **Yes, I fully agree with it.**

Q. **Did AGN 191103 help lead to the discovery that you made for which you filed your patent application?**

A. **No.**

Q. **Not at all?**

A. **No. It's a well-known fact in the formulation sciences that manipulating pH can change the nonionic, ionic balance. This isn't new. Plus, the 103 has a very different solubility profile to brimonidine in solution. And there are compounds that can exist in a nonionic state that are in solution. You don't need any solubilization system. This isn't new. This has been known for many, many**

years.

Q. **So you chose not to give it to the examiner?**

A. **Well, I don't know about that.**

Q. **I would also like you to look at JTX-054. That is the memo that yourself and Dr. Kerslake sent to Mr. Pfleger. Do you recall that?**

A. **I do.**

Q. **Dated June 9, 1998?**

A. **Unless it's something I don't have. That is something I don't have, I am sorry.**

Q. **I can let you borrow mine.**

THE COURT: That is fine.

BY MR. BOGGS:

Q. **I would like you to blow up the second page.**

Now, in this particular memorandum, it was indicated that the results from the rabbit studies for brimonidine did not translate into the Phase 2 studies. Do you recall that?

A. **Yes, that's in that fourth paragraph, I believe. Despite the observed bioavailability improvements of brimonidine Purite of .2 from animal pharmacokinetic studies, this was not reflected in the human Phase 2 studies.**

Q. **Now, did you ever figure out why those results did not translate into the Phase 2 studies with humans?**

A. **Well, when you do pharmacokinetic studies in animals, and the rabbit is the, normally the animal of choice, these are accessible, but it's known that there are differences between the rabbit and the human, although we do use animals, unfortunately, in the line of work that we are in, which we wouldn't, but we do.**

But we look at trends. And when you try to translate from the rabbit to the human, there are clearly different physiological effects.

Q. **Now, were you in the room when I gave my opening this morning?**

A. **Yes, I was.**

Q. **And did you hear my description of, with these kind of compounds, you have to do animal studies, and then you hope that the results of those animal studies translate into humans, then you have to do human studies, and there is costs associated with those and there is limitations on human studies? Did you hear me say that?**

A. **I don't know if you said those exact words. I would like to get away from the hope, there is a lot of hope in my life, but you try to go down a path of good, clear, scientific approach in the development of your products.**

Q. **What happened here in 1998, where your results from the animal studies did not translate into the human studies, is exactly an example of what I was talking about, a**

real-world example. Is that right?

A. There are occasions where you have a difference of effect from animal to human, those events do occur.

Q. Okay. If you would go back to the original claims that we were looking at, of your patent application?

MR. BOGGS: Your Honor, may I?

THE COURT: Yes, sir.

BY MR. BOGGS:

Q. Dr. Olejnik, we are looking at the original claims again. Now, original Claim 1 does not specify a concentration for the alpha-2-adrenergic agonist. Is that right?

A. It doesn't specify -- what was the question again?

Q. Original Claim 1 does not specify a concentration for the alpha-2-adrenergic agonist. Is that right?

A. Yes. It doesn't provide a number.

Q. In fact, none of the original 46 claims specify a concentration for the alpha-2-adrenergic agonist. Right?

A. I would have to go through and cross-check.

Q. We did this during your deposition. Do you recall that?

A. I recall the deposition.

Q. Do you recall what your answer was?

A. I would have to go back and look at the deposition notes.

Q. **Well, I think -- do we have the transcript up here?**

I believe your deposition transcript is there in front of you. I would like you to turn, if you would, to Page 15?

A. **Page 15?**

Q. **Yes. Day 2.**

You recall that I took your deposition. Right?

A. **Oh, yes.**

Q. **And you were under oath during that deposition?**

A. **Of course.**

Q. **Now, I would like you to confirm for me that during that deposition, I asked you the following question and you gave me the following answer.**

"Question: Now, do any of those 46 claims specify a concentration of the active ingredient?

"Answer: As a concentration, it does not specify that."

Did I ask you that question and did you give me that answer?

A. **It's at Page 15?**

Q. **16.**

A. **16?**

Q. **16.**

A. **I have Page 15 on the monitor. I am looking at the monitor.**

Could you repeat that again?

Q. **Yes. Please confirm for me, did I ask you the following question and you gave me the following answer:**

"Question: Now, do any of those 46 claims specify a concentration of active ingredient?

"Answer: As a concentration, it doesn't specify that."

A. **Yes, that's what I said.**

Q. **Did I ask you that question and did you give me that answer?**

A. **And that's the answer I gave you.**

Q. **Now, original Claim 1 also does not specify pH. Is that right?**

A. **No, it does not.**

Q. **Do you have a copy of the '834 patent in front of you?**

A. **Yes, I do. JTX-004.**

Q. **Look at Claim 1 of that patent, if you would?**

That claim specifies up to about 0.15 percent of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline tartrate.

Correct?

A. **Correct.**

Q. **And that's brimonidine tartrate. Right?**

A. **That is.**

Q. **That claim specifies a range of possibilities for brimonidine tartrate in terms of concentration. Is that**

right?

A. **What do you mean by "possibilities"? I am trying to understand the range of what possibilities.**

Q. **In terms of concentration, that claim provides for a number of different possibilities. Is that right?**

A. **It's a range of concentrations up to .15.**

Q. **So it provides for a number of different possibilities. Is that right?**

A. **Well, I am trying to understand what "possibilities" means.**

Q. **Do you understand what the word "possibilities" means?**

A. **I understand what possibility is, but in what context are you referring to it? That's what I am trying to understand.**

Q. **Does that claim embrace .14 percent?**

A. **Yes, it does.**

Q. **Does it embrace .02 percent?**

A. **.02 percent?**

Q. **Yes.**

A. **Up to and about .15, it's falling into that range, yes.**

Q. **All the way down to 0.02?**

A. **It says up to and about 0.15 percent.**

Q. **That claim would encompass 0.2 percent. Is that right?**

A. **In my understanding. I don't know what it would be from the legal profession.**

THE COURT: Counsel, let's take a break.

(Recess taken.)

THE COURT: Please be seated. Apologize, counsel, but it can't be helped. Mr. Boggs.

MR. BOGGS: Thank you, Your Honor. Can I have a read back?

(Pending question read.)

BY MR. BOGGS:

Q. **Dr. Olejnik, what is the lower limit of that range up to about 0.15 percent?**

A. **Well, it says up to and about 0.15 percent.**

Q. **What is the lower limit?**

A. **There is no lower limit that has been specified in terms of a number.**

Q. **How would we determine what that would be?**

A. **Well, if you look at the Claim 1, a therapeutically effective aqueous ophthalmic composition, you would want to have a therapeutically effective composition.**

Q. **What therapy is being referred to there?**

A. **Ophthalmic.**

Q. **Is the word "ophthalmic" in the original patent as filed, do you recall?**

A. **Did you ask me that question in the deposition?**

Q. **Do you recall?**

A. **No, I don't recall.**

Q. **Dr. Olejnik, do you know whether the words "glaucoma" or "intraocular pressure" are mentioned in the '834 patent?**

A. **Indirectly, if you go to the cited patent of Burke.**

Q. **Let's go to the cited patent of Burke.**

MR. BOGGS: May Mr. Suggs approach, Your Honor?

THE COURT: He may, yes.

BY MR. BOGGS:

Q. **I want to take you back for a minute to the '834 patent. Now, in Column 5, Lines 59 through 64, we have it up here on the screen, if that helps you.**

Have you seen that?

A. **Yes, I do.**

Q. **This is from your patent. It refers to the Burke et al. patent. The one you just asked for. Is that right?**

A. **There are a couple of Burke patents other than what is listed on the front page of the patent.**

Q. **This is the Burke patent that you incorporated in its entirety by reference. Do you see that?**

A. **Correct, yes.**

Q. **Do you believe this patent will tell us what therapy we should be talking about?**

A. **I would have to read them.**

Q. **Why don't you take a look, I will help you here, take**

a look at Column 1 of the Burke patent, the '077 Burke patent. And in particular, the first paragraph under the background of the invention, these are the therapies Burke notes. This has been incorporated into your patent, so this is part of your patent. Here, it says, "Methods of using such derivatives as therapeutic agents, to effect reduction in peripheral pain."

Is that just a pain reliever? Do you use it as a pain reliever?

A. **You would have to ask a clinician in terms of the definition. But reduction in peripheral pain, it can be ocular pain.**

Q. **That means ocular pain?**

A. **It can be pain. The way I read this, the way I interpret it, it would be an ocular injury that you would need to use some medication to reduce pain.**

Q. **Anesthetize the central nervous system. What does that mean?**

A. **You need to talk to a pharmacologist. But my understanding is it would be to provide an anesthetic effect to the CNS.**

Q. **To constrict one or more blood vessels, what does that mean?**

A. **To reduce the size of a blood vessel.**

Q. **Is that like an Epigen, something like that?**

A. **You may want to constrict blood vessels in the eye. If you have red eye from being on a plane, vasoconstrictors, you have a class of compounds that have been used. You may want to relieve the retinas.**

Q. **To treat ischemia. What does that mean?**

A. **That is for the heart.**

Q. **To decongest one or more nasal passages. What does that mean?**

A. **Open up the nasal pathways. There has been work done in the field of ophthalmic looking at delivering drugs to have an effect on the nasal passages by ophthalmic products.**

Q. **And to effect reduction of one or more effects of an inflammatory disorder to increase renal fluid flow and to effect an alteration in the rate of fluid transport in the gastrointestinal tract. What are those?**

A. **You would have to talk to a clinician, pharmacologist specific to that.**

Q. **This is part of your patent. Is glaucoma included somewhere in here?**

A. **There is nothing related to intraocular pressure. But it doesn't relate to using the product for other aspects of treating certain ophthalmic diseases.**

Q. **When was Alphagan P launched as a product?**

A. **I don't remember.**

Q. **Was it in --**

A. **I think it was --**

Q. **2000?**

A. **I think it was March or April of, I forget the date now.**

Q. **How is it that you could file the patent application without the -- for the '834 patent and never mention the word "glaucoma" or "intraocular pressure"?**

A. **I don't know. You would have to talk to the patent attorneys on that.**

Q. **Therapeutically effective in Claim 1 of the '834 patent could be for treating an inflammatory disorder or to increase renal fluid. That's what's in your patent application. Is that right?**

A. **Well, as contained, as extracted from that, yes. Again, you can use ophthalmic products that have been shown and developed to target other areas through the eye, where it has been considered in those areas, as another route of administration.**

MR. BOGGS: Can I have a moment?

THE COURT: Yes.

(Pause.)

BY MR. BOGGS:

Q. **I want to look at the curve at Figure 1 of the '834 patent. What does this curve indicate?**

A. **As I just said earlier, that this is a solubility**

profile of brimonidine tartrate and pH in the presence of CMC and without CMC.

Q. What was the formulation of formulation used to generate this data?

A. I would have to go to the actual study itself.

Q. It's actually in Column -- or Table 3 and Table 4. Right?

A. It came out of the Table 3, Table 4 work that was done.

Q. And each of those formulations that are listed in Table 3, sample one, sample 2, sample 3, sample 4, sample 5, each of those is a .2 percent formulation. Is that right?

A. Well, it says .2 percent, that's correct. But one needs to understand, in terms of an equilibration study, someone that is familiar in the art understands that you have to have a saturated amount of drug presence.

Q. Do you recall an experimental formulation at Allergan with the designation 9115 X? Do you recall that?

A. I would have to look at the "X" number.

Q. Now, you told me at your deposition that the curve in Figure 1 was 0 percent CMC. That's the first curve on the left. Right?

A. That is correct.

Q. That could -- that particular curve could support all possible concentration range for active ingredient. Is that

right?
A. On that line?
Q. Yes.
A. For each specific dot, it would support in the absolute sense, but in the real sense, in dealing with a product that has excursions in pH, it wouldn't. But in the absence, yes.
Q. I would like you to take a look at your transcript, if you would. Page 22. Line 21.
A. Okay.
Q. Please confirm for me that I asked the following question and that you gave me the following answer:
"So if you look at the curve with zero percent CMC, what's the range that that supports for an active ingredient?
"THE WITNESS: It can support any range."
Did I ask you that question and did you give me that answer?
A. Yes, I did.
Q. Now, looking back at Claim 1 of the '834 patent, that claim also contains a range specified as about 7.0 or greater. Correct?
A. In Claim 1?
Q. Yes.
A. That's correct, yes.

Q. **And none of the original claims use those words, "about 7.0 or greater." Is that right?**

A. **That's correct.**

Q. **And the original specification never used those words, either. Right?**

A. **I would have to go back and verify. But I believe that that is correct, yes.**

Q. **Now, the brimonidine X project started in January of 1997. Is that right?**

A. **That's when it got elevated as a project.**

Q. **And at various times, the brimonidine team had different lead formulations. Is that right?**

A. **Different prototype formulations being assessed, correct.**

Q. **Different lead formulations?**

A. **We do have lead formulations that we assess and prototype formulations, leads emanate out of prototype.**

Q. **And the .15 percent formulation, which corresponds to Alphagan P, became the lead formulation on May 29th, 1998. Is that right?**

A. **I believe that is correct.**

Q. **And this came about after looking at a number of other formulations. Is that right?**

A. **Yes.**

Q. **And as you went through a screening process, you moved**

towards this final lead formulation that you took in the Phase 3 trials. Is that right?

A. Could you repeat that again, please.

Q. As you went through the screening process, you moved towards this final lead formulation which you then took into the Phase 3 trials. Right?

A. Yes, on one of them, yes.

Q. And that was Alphagan P .15 percent. Right?

A. It was .15. It was .2 as well.

Q. In the '834 patent, there was no composition table that talks about .15 percent and lists the components part of Alphagan P. Is that right?

A. Could you repeat that again?

Q. In the '834 patent, there is no composition table that talks about a .15 percent formulation and lists the components of Alphagan P. Is that correct?

A. Well, there is no table listed in here, but you can, by knowledge, define the .15.

Q. It does disclose a .2 formulation. Is that right?

A. Are you referring to Table 3?

Q. Yes.

A. It says .2. But in a pH solubility study, you need to saturate a system. Anyone that is familiar in conducting pH solubility studies will know that one would have to have saturated systems. And when you are dealing with looking at

a pH in acidic conditions, you are going to add in even more brimonidine. That is going to be a known fact. It's just that it got listed as .2.

But anyone with an understanding in pH solubility profiles and studies thereof fully understands that you have to have saturated systems, they need to be equilibrated, and you have to have enough drug in there to achieve that saturated state.

Part of the reason when you run studies within the pharmaceutical companies, one has to be careful in how much drug you begin to add. You do want to have a saturated state. If you are dealing with a very, very expensive drug, you don't waste too much. So you build, build, and build.

Q. So you have more than .2 percent?

A. In the studies that we conducted, there would have been more than .2.

Q. Now, in our claim, we have up to about .15 percent. Right?

A. That is correct.

Q. And that's less than .2 -- or .2-plus. Right?

A. Yes.

THE COURT: Mr. Boggs, about how much more do you think you have?

MR. BOGGS: Maybe five minutes.

THE COURT: Okay.

MR. BOGGS: At most.

BY MR. BOGGS:

Q. **Now, back in the '834 patent, Table 2, you talked about that a little earlier today. Do you recall discussing that this morning?**

A. **Yes, I do. This afternoon.**

Q. **And there is an error in there, in this table?**

A. **Yes.**

Q. **I thought I heard you say this morning that this table includes results from some prior work that existed when you got involved in the project. Is that right?**

A. **No, I didn't say anything this morning.**

Q. **Where did this data come from?**

A. **This came from a study under Shulin Ding. It was a Scott Jordan study, I believe.**

Q. **But this isn't work that you did. Right?**

A. **No.**

Q. **And, in fact, this is a -- this is work from a .5 percent formulation. Right?**

A. **I need to go back to the study.**

Q. **Okay. Well, let's look at Column 14 of the patent. And we have Table I and Table II. And confirm for me that Table II has the solubility results from Table I.**

Here you have .5 percent, is that .5 percent?

A. **In Table I?**

Q. **Yes, for brimonidine tartrate?**

A. **Yes, it says, Brimonidine tartrate, .5 percent.**

Q. **And benzalkonium chloride, .0050?**

A. **Yes.**

Q. **Polyvinyl alcohol, do you see that?**

A. **Yes, I do.**

Q. **Sodium chloride, and you have the citrate buffers?**

A. **Yes.**

Q. **Sodium hydroxide, and purified water?**

Is that the .5 percent formulation that Allergan submitted an NDA on in 1996?

A. **An NDA?**

Q. **Yes.**

A. **I don't remember. I will have to go back and check. I submitted an NDA on .2 percent for Alphagan. I would have to go back and check on the .5.**

Q. **You don't know one way or another whether they submitted a .5 percent NDA at the same time as --**

A. **I would have to go back and -- it's, again, in the early stages of my joining with Allergan at the time.**

MR. BOGGS: I don't have any further questions.

THE COURT: Thank you, Mr. Boggs. We will resume tomorrow at 9:00.

(Court recessed at 5:01 p.m.)